DISSERTATION ZUR ERLANGUNG DES DOKTORGRADES
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Studies Toward the Total Syntheses of Waixenicin A and Jerantinine E

von

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Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Thomas Magauer betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfsmittel erarbeitet.

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Tatjana Huber

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To my parents and Johannes

"Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as an excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective."

Robert Burns Woodward, *Proc. Robert A. Welch Foundation Conf. Chem. Res.* **1969**, *12*, 3.

Parts of this thesis have been published in peer-reviewed journals:

"Development of a β-C–H Bromination Approach toward the Synthesis of Jerantinine E" – T. Huber,† T. A. Preuhs,† C. K. G. Gerlinger, T. Magauer, *J. Org. Chem.* **2017**, 82, 7410−7419.

"Synthesis of Xenia Diterpenoids and Related Metabolites Isolated from Marine Organisms" – T. Huber,† L. Weisheit,† T. Magauer, *Beilstein J. Org. Chem.* **2015**, *11*, 2521−2539.

"Experimental Studies on the Selective β-C–H Halogenation of Enones" − T. Huber, D. Kaiser, J. Rickmeier, T. Magauer, *J. Org. Chem.* **2015**, *80*, 2281−2294.

† Equal contributors.

Parts of this thesis have been presented at scientific conferences:

"*Studies toward the total synthesis of waixenicin A – a selective TRPM7 inhibitor*" (poster), T. Huber, T. Magauer. TRR 152 Symposium, Herrsching, Germany, October 2015.

"Experimental Studies on the Selective β-C−H Halogenation of Enones" (poster), T. Huber, D. Kaiser, J. Rickmeier, T. Magauer. Heidelberg Forum of Molecular Catalysis 2015, Heidelberg, Germany, June 2015.

Zusammenfassung

Diese Doktorarbeit beschreibt unsere Studien zu den Totalsynthesen des marinen Diterpenoids Waixenicin A (Teil I) und des Alkaloids Jerantinin E (Teil II).

Teil I: Waixenicin A ist ein *Xenia* Diterpenoid, das aus der hawaiianischen Oktokoralle *Anthelia edmondsoni* isoliert wurde. Dieser Sekundärmetabolit ist ein selektiver und wirkungsvoller TRPM7 Ionenkanalblocker und somit ein potentielles Krebsmedikament. Waixenicin A hat darüber hinaus ein sehr interessantes Molekülgerüst mit einer 6,9-bizyklischen Grundstruktur, die sich wiederum aus einem Dihydropyran mit drei aufeinander folgenden stereogenen Zentren und einem (*E*)-konfigurierten Cyclononen-Fragment zusammensetzt. Waixenicin A gehört zur Xenicin Unterfamilie der *Xenia* Diterpenoide und konnte trotz seiner bemerkenswerten biologischen Wirkung und faszinierenden Molekülstruktur bisher noch nicht totalsynthetisch hergestellt werden.

Der erste Teil dieser Doktorarbeit beschreibt die erfolgreiche Entwicklung einer praktischen und enantioselektiven Syntheseroute für die bizyklische Kernstruktur von Waixenicin A. Die erarbeitete Route begann mit der Verknüpfung der zwei Bausteine **I** und **II** mittels einer dreistufigen Synthesesequenz (Michael-Addition, Mukaiyama-Aldoladdition, Formaldehyd-abspaltung). Die Einführung der Stereozentren in Position C2 und C3 wurde dabei durch das Stereozentrum in Position C18 gesteuert. Als Nächstes wurde eine intramolekulare α-Alkylierung eines Phenylsulfon-Anions mit einem allylischen Bromid dazu verwendet um das 6,9-Grundgerüst aufzubauen, das nicht nur in Waixenicin A, sondern auch in vielen anderen Xenicinen zu finden ist.

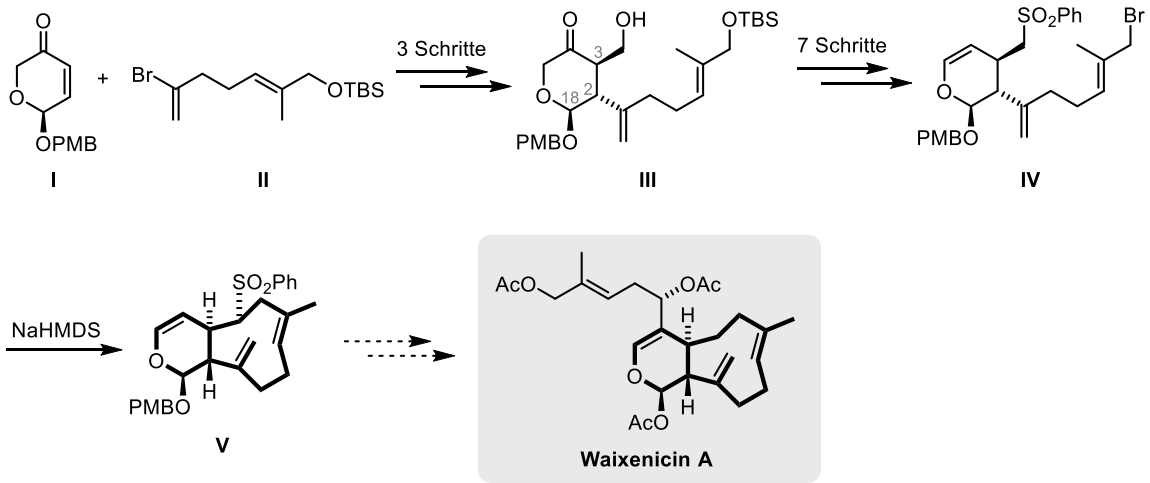


Abbildung A. Kurze und konvergente Syntheseroute für die Kernstruktur von Waixenicin A.

Teil II: Der zweite Teil dieser Doktorarbeit beschäftigt sich mit dem Monoterpen-Indolalkaloid Jerantinin E, das aus der malaysischen Pflanze *Tabernaemontana corymbose* isoliert wurde. Dieser Sekundärmetabolit gehört zur Familie der *Aspidosperma* Alkaloide und besitzt ein komplexes pentazyklisches Kohlenstoffgerüst mit einer Indolstruktur. Jerantinin E ist ein vielversprechendes Zytostatikum, dessen Wirkung auf Hemmung der Tubulin-Polymerisation beruht. Seit vielen Jahrzehnten sind Monoterpen-Indolalkaloide beliebte Zielmoleküle für Synthesechemiker. Aufgrund ihrer strukturellen Komplexität und ihren vielfältigen biologischen Wirkungen wurden bereits viele dieser Naturstoffe in der Vergangenheit synthetisch hergestellt.

Unsere Synthesestrategie für Jerantinin E basierte auf der Verwendung unserer kürzlich entwickelten Eintopf-Methode für die selektive *β*-Bromierung von zyklischen Enonen. Damit sollte die Syntheseroute für das trizyklische Tetrahydrocarbazolon-Fragment im Vergleich zu bisherigen Routen verkürzt werden. In unseren Studien wurde eine skalierbare und robuste Route für die Synthese des funktionalisierten Tetrahydrocarbazolons **IX** ausgehend von Enon **VI** entwickelt. Die Indolstruktur wurde mittels Palladium-katalysierter Aminierung und anschließender Palladium-katalysierter oxidativer Indolsynthese aufgebaut. Die weitere Funktionalisierung des Zwischenprodukts **VIII** führte dann zur Synthese von Tetrahydrocarbazolon **IX**, das bereits alle Kohlenstoffatome von Jerantinin E besitzt.

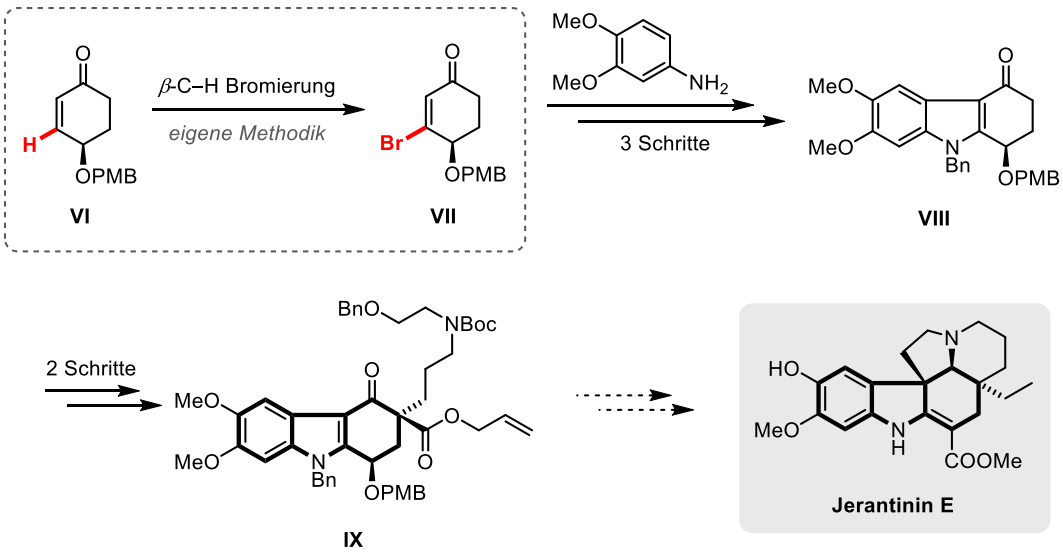


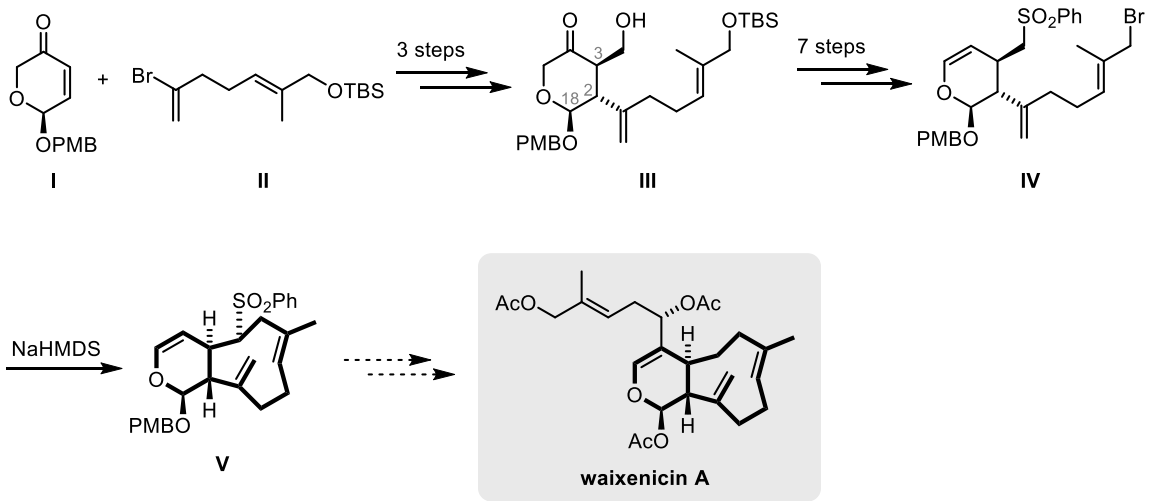
Abbildung B. Kurze Synthese eines funktionalisierten Tetrahydrocarbazolons für die Totalsynthese von Jerantinin E.

Abstract

This Ph.D. thesis describes progress toward the total syntheses of the marine diterpenoid waixenicin A (part I) and the alkaloid jerantinine E (part II).

Part I: Waixenicin A is a *Xenia* diterpenoid isolated from the octocoral *Anthelia edmondsoni*, collected on Hawaiian shores. This secondary metabolite was found to act as a selective and potent TRPM7 ion channel inhibitor, which makes it a potential chemotherapeutic agent. Waixenicin A furthermore possesses an interesting molecular scaffold, comprising a 6,9-bicyclic framework with a dihydropyran ring with three contiguous stereogenic centers *trans*-fused to an (*E*)-configured cyclononene. Waixenicin A belongs to the xenicin subclass of the *Xenia* diterpenoids and despite its remarkable bioactivity and fascinating structure, no total synthesis has been reported to date.

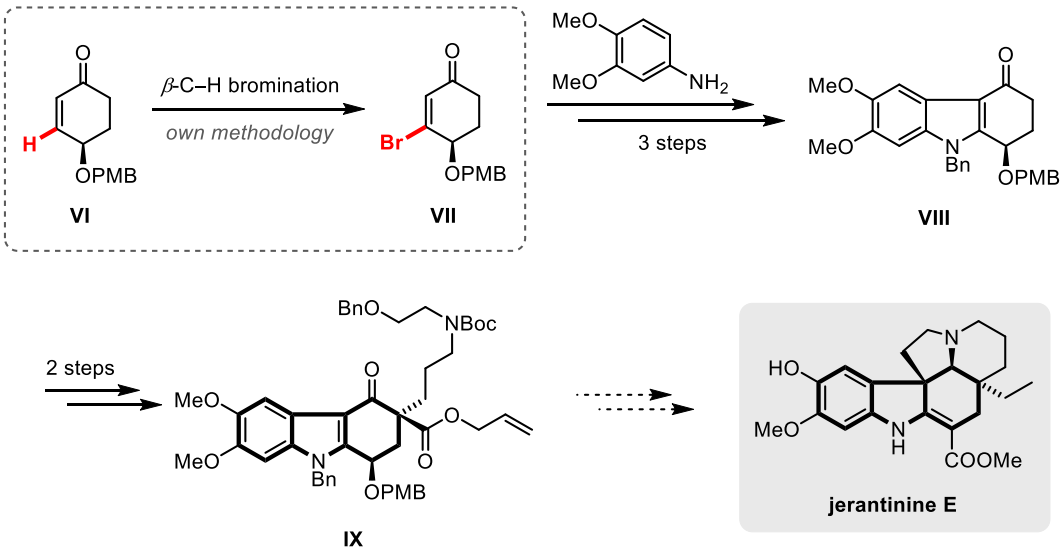
The first part of this thesis describes our successful efforts in developing a practical and enantioselective synthetic route to the bicyclic core structure of waixenicin A. The elaborated route commenced with the assembly of the two building blocks **I** and **II** by a three-step sequence (conjugate addition, Mukaiyama aldol reaction, formaldehyde extrusion). The stereocenter at C18 thereby directed introduction of the two contiguous stereocenter at C2 and C3. Next, an intramolecular α-alkylation of a phenylsulfonyl anion onto an allylic bromide was devised to produce the 6,9-framework **V** of waixenicin A, which is also commonly found in several other xenicin members.



Scheme A. Convergent and short synthesis of the core structure of waixenicin A.

Part II: The second part of this thesis focuses on with the monoterpene indole alkaloid jerantinine E, isolated from the Malayan plant *Tabernaemontana corymbose*. This secondary metabolite belongs to the *Aspidosperma* alkaloid family and comprises a complex pentacyclic carbon skeleton with an indole substructure. Jerantinine E was found to be a potent chemotherapeutic agent that acts by inhibiting tubulin polymerization. Monoterpene indole alkaloids have been attractive targets for synthetic chemists for several decades due to their structural complexity and diverse biological activities and many of these unique natural products have been synthesized in the past.

Our synthetic efforts toward jerantinine E were based on the utilization of our recently developed one-pot procedure for the selective *β*-bromination of cyclic enones. Thereby, the synthetic route for the tricyclic tetrahydrocarbazolone fragment could be achieved in a more concise manner compared to previously reported approaches. A scalable and robust synthetic approach to functionalized tetrahydrocarbazolone **IX** was developed starting from readily prepared enone **VI**. The indole substructure of the natural product was then installed by palladium-catalyzed amination and subsequent palladium-catalyzed oxidative indole formation. Functionalization of intermediate **VIII** afforded tetrahydrocarbazolone **IX**, which already contained all carbon atoms of jerantinine E.



Scheme B. Short synthesis of a functionalized tetrahydrocarbazolone en route to jerantinine E.

Acknowledgements

A doctoral thesis is often seen as a solitary endeavor; however, the long list that follows proves the opposite. My time as a Ph.D. student has certainly been the most interesting and challenging period of my life and many great people accompanied me on this journey.

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List of Abbreviations

Å	Ångström
°C	degrees Celsius
δ	chemical shift in ppm downfield relative to a standard
Ac	acetyl
AIBN	1,1′-azobis(isobutyronitrile)
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
Calcd	calculated
CAM	ceric ammonium molybdate(IV)
cat.	catalytic
CBS	Corey−Bakshi−Shibata
CCDC	Cambridge Crystallographic Data Centre
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
cod	1,5-cyclooctadiene
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DFT	density functional theory
DIBALH	diisobutylaluminium hydride
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine (Hünig's base)
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DMP	Dess−Martin Periodinan
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron ionization

equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
ESI	electrospray ionization
e.g.	*exempli gratia* (for example)
g	gram
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HR-MS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
-i	*iso*
IC_{50}	half maximal inhibitory concentration
imH	imidazole
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LDA	lithium diisopropylamide
MABR	methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Min	minutes
mL	milliliter
mmol	millimole
MoOPH	oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)
MS	molecular sieves
MsCl	mesylsulfonyl chloride
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
OMe	methoxy
p	*para*

Pd/C	palladium on charcoal
PG	protecting group
Ph	phenyl
Ph.D.	Doctor of Philosophy
PhH	benzene
PhMe	toluene
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
py	pyridine
quant.	quantitative
R*f*	retardation factor (TLC)
SOMO	single occupied molecular orbital
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
T	temperature
T	time
t-	*tert*
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCDI	1,1’-thiocarbonyldiimidazol
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TRPM7	transient receptor potential melastatin 7
TTMSS	tris(trimethylsilyl)silane)
UV	ultraviolet
wt%	weight percent

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Part I: Studies Toward the Total Synthesis of Waixenicin A

Part II: Studies Toward the Total Synthesis of Jerantinine E

Experimental Part

PART I

Studies Toward the Total Synthesis of Waixenicin A

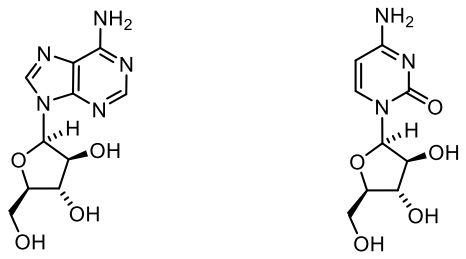
1 Introduction

1.1 General Introduction

Natural products have long been a traditional source of medicines. Isolated from terrestrial plants and microorganisms, natural products are usually secondary metabolites. While secondary metabolites are not essential for organisms, they generally serve survival functions to the organism including defense against other competing organisms and/or agents of symbiosis. The isolation of the pain reliever morphine from poppy straw[1] and the discovery of the first antibiotic penicillin from mold[2] are early examples for highly bioactive natural products that have been marketed as drugs. Over the last decades, pharmacologically active compounds from plants and microbes have played an important role for drug discovery. From the 1940s to 2006, 47% of all approved anti-cancer agents worldwide have been "*either natural products or directly derived therefrom*".[3]

1.2 Marine Natural Products as a Source of New Drugs

The isolation of the first marine natural product was reported in 1940.[4] While only few compounds from the sea were isolated and reported in the next 30 years, Werner Bergman reported the isolation of unusual *arabino*- and *ribo*-pentosyl nucleosides in the 1950s from marine sponges collected in Florida, USA.[5–7] The discovery of these compounds ultimately led to the development of two sugar modified nucleoside analogs, vidarabine (**1**) and cytarabine (**2**) (Figure 1).[8] Vidarabine (**1**) (brand name: Vira-A®) is a diastereomer of adenosine with the D-ribose replaced with D-arabinose. It was later the first agent to be approved for the treatment of systematic herpes virus infection in humans. Cytarabine (**2**) (brand name: Cytosar-U®) is a diastereomer of cytidine and an anti-metabolic agent that is used for treatment of different forms of leukemia.

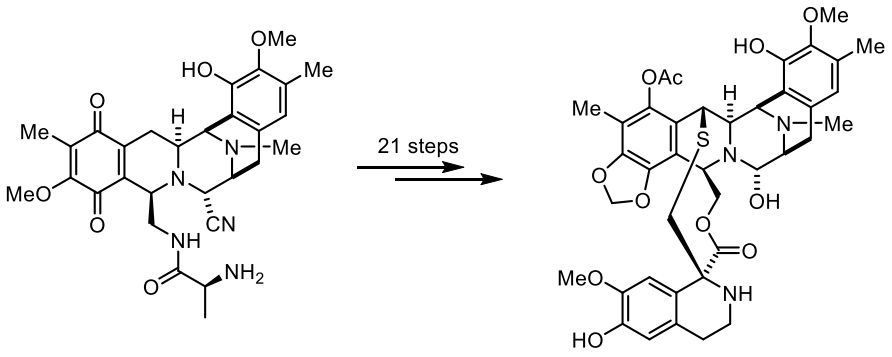


vidarabine (**1**) cytarabine (**2**)

Figure 1. The sugar modified nucleosides vidarabine (**1**) and cytarabine (**2**).

The systematic exploration of the oceans only began in the mid-1970s when modern snorkeling and scuba diving techniques emerged. The number of reported marine natural products rapidly increased and by 2013, a total amount of 23,750 natural products isolated from marine organisms

has been reported.[9] The remarkable biological activities of marine natural products led to an increased interest of several pharmaceutical companies. However, the sustainable harvesting of significant amounts of the source organism remained the major challenge. The relatively low natural abundance of most of the bioactive compounds and the fact that many marine organisms, such as corals and sponges, are largely unculturable, make the development of drugs from marine natural products difficult. Additionally, extensive harvesting of wild marine invertebrates would have a huge impact on the marine environments. In order to solve this supply problem, several possible solutions ranging from total synthesis or semi-synthesis to aquacultures of marine organisms have to be taken into consideration. Given all these difficulties, it took several decades before the first marine-derived natural product was approved in the United States. In 2004, ziconotide (brand name: Prialt®) was approved for the treatment of severe and chronic pain.[10] The peptide is the synthetic version of an ω-conotoxin peptide, which was found in the toxic venom of the tropical cone snail *Conus magnus*. The approval of the first marine-derived anti-cancer agent, ecteinascidin 743 (**4**) (brand name: Yondelis®), was a significant milestone in 2007. The anti-tumor properties of this tetrahydroisoquinoline alkaloid, isolated from the Caribbean sea-squirt *Ecteinascidia turbinata*, were first reported in 1969. Unfortunately, ecteinascidin 743 (**4**) was one of the least abundant compounds (~10 ppm) of the organism and it took more than 20 years before the structures of the active compounds, the ecteinascidins, were finally elucidated.[11,12] The first enantioselective total synthesis of ecteinascidin 743 (**4**) was achieved by E. J. Corey in 1996[13] and several other synthetic approaches have been published since then.[14–16] However, owning to the complex structure of ecteinascidin 743 (**4**), total synthesis was not the key to success in preparing sufficient amounts for clinical trials. Nevertheless, the development of a synthetic route for the total synthesis of ecteinascidin 743 (**4**) led to the discovery of the synthetic derivative phthalascidin with comparable antitumor properties.[17] A major breakthrough was then achieved by the company PharmaMar who could finally access ecteinascidin 743 (**4**) via large scale semi-synthesis from cyanosafracin B (**3**), an antibiotic of bacterial origin which can be prepared by fermentation of the bacteria *Pseudomonas fluorescens* (Scheme 1).[18]



Scheme 1. The gram-scale production of ecteinascidin 743 (**4**) from cyanosafracin B (**3**) by PharmaMar.

Today, eight marine natural product derived compounds are on the market with only three of them being the original natural product.[19] Besides ziconotide (Prialt®) and ecteinascidin 743 (Yondelis®), Iota-carrageenan (Carragelose®), a linear sulphated polysaccharide isolated from *Rhodophyceae* seaweeds, is marketed as an anti-viral nasal spray. The other five compounds became drugs after modification of the original natural products. Besides the nucleoside analog cytarabine (**2**, Cytosar-U®) and the natural product ecteinascidin 743 (**4**, Yondelis®), two additional marine natural products derivatives are on the market as anti-cancer agents. The halichondrin B analog eribulin mesylate (Halaven®) is an anti-cancer drug that is mainly used for the treatment of metastatic breast cancer. Brentuximab vedotin 63 (Adcetris®) was approved for the treatment of Hodgkin and systemic anaplastic large cell lymphoma and is a synthetic analog of dolastatin 10 linked to an anti-CD30 antibody. The last example for FDA-approved marine natural product derived drugs is Lovaza®, a group of ethyl esters of several omega-3 fatty acids from fish oils that is used as an anti-hypertriglyceridemia drug. Several other compounds of marine origin are currently in different phases of the clinical trial and an overview on these compounds is given in Table 1.[20]

Table 1. Marine natural products and derivatives in clinical development (Phase II and III).[20]

Entry	Compound name	Chemical Class	Source	Disease area	Status
1	Halichondrin B (**5**)	Polyether macrolide	Sponge	Cancer	Phase III
2	Soblidotin (**6**)	Peptide	-[a]	Cancer	Phase III
3	Tetrodotoxin (**7**)	Alkaloid	Fish	Cancer-associated pain	Phase II/III
4	DMXBA (**8**)	Alkaloid	-[b]	Central nervous system	Phase II
5	Plitidepsin	Peptide	Tunicate	Cancer	Phase II
6	Elisidepsin	Peptide	-[c]	Cancer	Phase II
7	PM00104	Alkaloid	-[d]	Cancer	Phase II
8	Plinabulin (**9**)	Diketopiperazine	Marine fungi	Cancer	Phase II
9	ILX-651	Peptide	-[e]	Cancer	Phase II
10	Pseudopterosin A (**10**)	Diterpene glycoside	Coral	Wound healing Inflammation	Phase II

[a]Synthetic derivative of dolastatin 10. [b]Synthetic imitative of anabaseine. [c]Synthetic analog of the kahalalide family. [d]Semi-synthetic analog of jorumycin. [e]Synthetic analog of dolastatin-15.

The structures of selected compounds are shown in Figure 2.

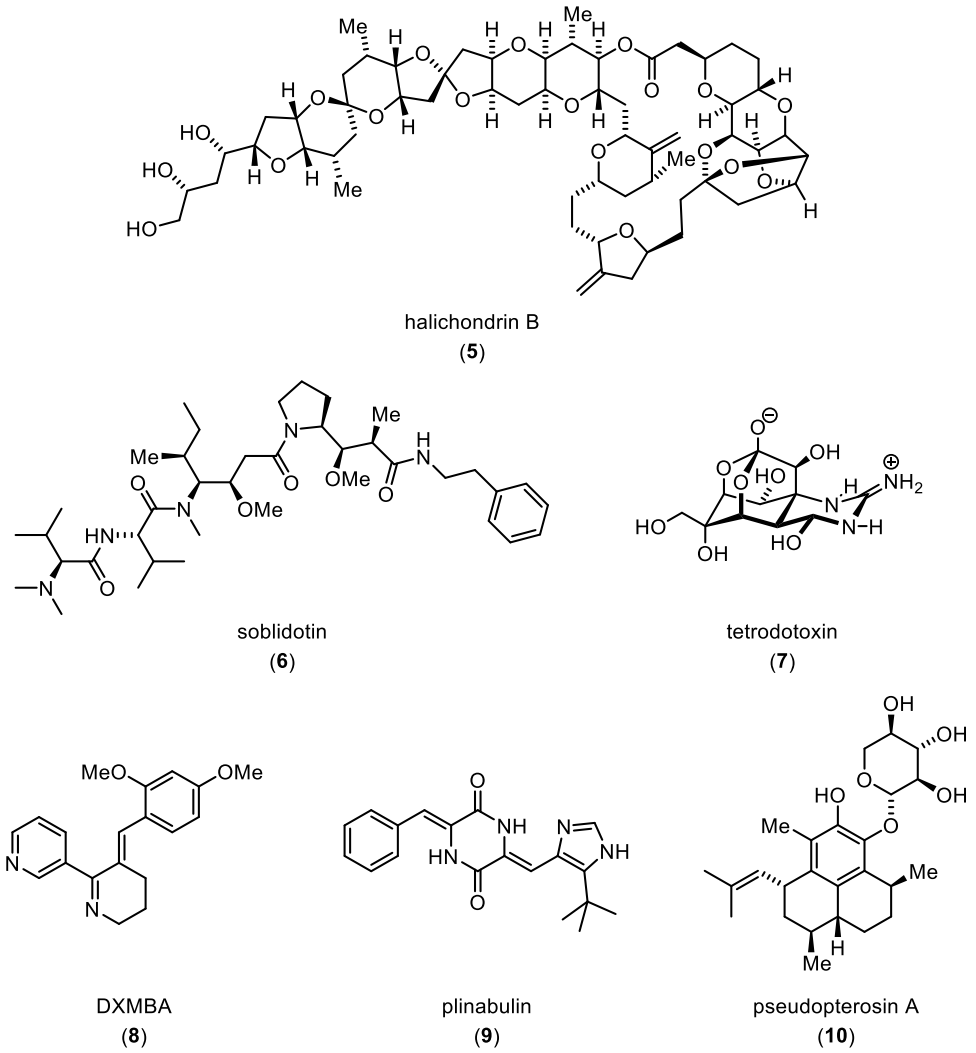


Figure 2. Structures of selected natural products and natural product derived compounds that are currently in phase II or III clinical trials.

These examples demonstrate that the field of marine natural products remains highly interesting for the pharmaceutical industry. Furthermore, it was recently found that many natural products isolated from marine macroorganisms, such as sponges and tunicates, are synthesized by symbiotic bacteria that live with the larger host organisms.[21] Most of these symbionts are as-yet unculturable, but these microorganisms can definitely be seen as a valuable source for the discovery of unknown natural products.

1.3 Soft Corals of the Genus *Xenia*

Soft corals are a rich source of highly bioactive secondary metabolites. They are filter feeding invertebrates that harvest plankton from the water. Most coral colonies live in symbiosis with the single-celled planktonic organism zooxanthellae.[22] Zooxanthellae are photosynthetic organisms and their photosynthetic pigments are responsible for the bright colors of the soft corals. They are

essential for the survival of their host colonies and provide the corals with carbohydrates which are needed for the corals' growth, metabolism and reproduction. As compared to hard corals, soft corals lack a protective calcium carbonate skeleton. Furthermore, they possess a very simple immune system. Their defense strategy against predators relies on the production of chemical compounds that renders the corals unpalatable. Additionally, chemicals are produced to inhibit the growing of other organisms that compete for food and light.[23] Due to the high dilution of these compounds in the water, it is not surprising that numerous bioactive compounds have been isolated from soft corals. Current studies on these compounds revealed that at least some secondary metabolites isolated from soft corals are produced by their symbiotic partners and not by the corals themselves.[24]

One example for soft corals that have been a rich source of bioactive natural products are the members of the genus *Xenia* (order *Alcyonacea*, family *Xeniidae*) (Figure 3).

Figure 3. Images of soft corals of the genus *Xenia*: *Xenia umbellata*[*] (left) and *Xenia sp.*[†]

The *Xenia* genus includes 28 species that live in the shallow water of tropical reefs in the Indo-Pacific. These corals are producers of diterpenoids, the so-called *Xenia* diterpenoids, that exhibit a variety of anti-cancer and anti-microbial activities.[25]

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1.4 Synthesis of *Xenia* Diterpenoids and Related Metabolites Isolated from Marine Organisms

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Synthesis of *Xenia* diterpenoids and related metabolites isolated from marine organisms

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Review

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Abstract

This review describes strategies for the chemical synthesis of xenicane diterpenoids and structurally related metabolites. Selected members from the four different subclasses of the *Xenia* diterpenoid family, the xenicins, xeniolides, xeniaphyllanes and xeniaethers, are presented. The synthetic strategies are discussed with an emphasis on the individual key reactions for the construction of the uncommon nine-membered carbocycle which is the characteristic structural feature of these natural products. Additionally, the putative biosynthetic pathway of xenicanes is illustrated.

Introduction

Terpenoids are a large group of structurally diverse secondary metabolites. Among these natural products, *Xenia* diterpenoids or xenicanes represent a unique family with intriguing structural features and diverse biological activities. Many xenicanes display significant cytotoxic and antibacterial activity and are therefore of great interest for drug discovery, especially for their application as anticancer agents [1]. Marine soft corals of the genus *Xenia* (order *Alcyonacea*, family *Xeniidae*) are known to be rich in xenicane diterpenoids. The first reported member of these metabolites was xenicin (**1**), isolated from the soft coral *Xenia elongata* in Australia, whose structure was elucidated in 1977 by Schmitz and van der Helm (Figure 1a) [2]. The common numbering of the xenicane skeleton shown in Figure 1b is used throughout this review.

Since then, several further xenicanes with various modifications of the cyclononane ring and isoprenyl side chain in their structure have been isolated. In general, the common structural feature of xenicanes is a bicyclic framework consisting of an A ring which is trans-fused to a nine-membered carbocyclic B ring. The family of *Xenia* diterpenoids was originally divided into three subfamilies: the xenicins (containing an 11-oxabi-

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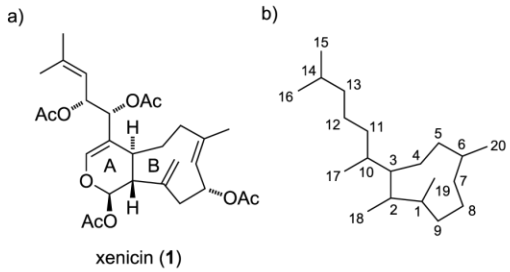

Figure 1: a) Structure of xenicin (**1**) and b) numbering of the xenicane skeleton according to Schmitz and van der Helm.

cyclo[7.4.0]tridecane ring system with an acetal functionality) [2], the xeniolides (containing an 11-oxabicyclo[7.4.0]tridecane ring system with a lactone functionality) [3] and the xeniaphyllanes (with a bicyclo[7.2.0]undecane ring system) [4]. Later, an additional subfamily was discovered and named xeniaethers [5] (containing an 11-oxabicyclo[7.3.0]dodecane ring system). An overview of representative members of these subfamilies is depicted in Figure 2.

Xenicanes are closely related to a number of metabolites which also feature the characteristic cyclononene framework (Figure 3). For example, a class of bicyclic sesquiterpenes, caryophyllenes [21], exhibit the same bicyclo[7.2.0]undecane skeleton as xeniaphyllanes. Furthermore, while monocyclic azamilides [22] are seco-A-ring diterpenoids that are acylated with fatty acids, *Dictyota* diterpenes [23,24] either bear a similar seco-ring fragment, as observed for dictyodiol (**24**), or comprise a fused γ-butyrolactone moiety, as in dictyolactone (**25**, Figure 3).

This review intends to provide a comprehensive overview of research covering xenicane diterpenoids and related natural products. In the following section, we present a biosynthetic proposal, discuss various synthetic approaches towards xenicane diterpenoids and highlight successful total syntheses.

Review

Biosynthetic hypothesis

The proposed biogenesis of xenicanes (Scheme 1) is suggested to be similar to the reported biosynthesis of the structurally related caryophyllene sesquiterpenes [25]. *Xenia* diterpenoids are believed to originate from the common diterpenoid precursor geranylgeranyl pyrophosphate (GGPP, **28**), which is assembled from the two terpene units, isoprenyl pyrophosphate (IPP, **26**) and dimethylallyl pyrophosphate (DMAPP, **27**) [26]. Initial loss of a diphosphate anion from GGPP generates an allylic cation in **29** which is intramolecularly trapped by nucleophilic attack of the C3,C10-double bond, forming the secondary cation **30**. Attack of the newly generated C1,C2-double bond with simultaneous loss of a proton then affords the bicyclo[7.2.0]undecane ring system **31** as found in xeniaphyllanes [3]. Finally, double C–H oxidation furnishes the β-hydroxy aldehyde **32** which can undergo a retro-aldol reaction with concomitant opening of the cyclobutane ring to form dialdehyde **33** as the common biogenetic precursor of xenicins, xeniolides and xeniaethers.

An alternative biosynthetic pathway proposed by Schmitz and van der Helm involves the direct formation of the nine-membered carbocyclic ring via oxidative cyclization of geranyllinalool (**34**) [2], which is formed from GGPP (**28**) by enzymatic hydrolysis of the pyrophosphate unit and allylic rearrangement (Scheme 2).

Synthetic strategies

The unusual molecular structures and the potential of xenicanes to act as chemotherapeutic agents make these natural products attractive targets for synthetic chemists. Although more than 100 different *Xenia* diterpenoids are known to date, only a few total syntheses of xeniolides have been reported in the last two decades. Surprisingly, since the discovery of xenicin in 1977 [2], no total synthesis of a member of this subclass has been accomplished.

The synthesis of nine-membered rings is challenging, especially when they contain an *E*-configured double bond. Different strategies for the construction of *E*- or *Z*-cyclononenes have been reported to date and common reactions are summarized in Scheme 3. Transition metal-catalyzed ([M] = Ru, Mo, W) ring-closing metathesis (RCM) reactions of 1,10-dienes **A** can be employed for the synthesis of cyclononenes. The *E*/*Z*-selectivity of the olefin depends on the ring-size and the choice of catalyst. As a consequence of avoiding ring strain, small- and medium-sized rings are generally obtained with *Z*-configuration of the alkene. The Grob fragmentation reaction of fused 6,5-bicycles **B** is usually a concerted process that affords cyclononenes in a stereospecific manner [27]. The relative configuration of the leaving group (LG = OTs, OMs, Hal, NR_3^+) and the adjacent substituent determine the *E*/*Z*-geometry of the olefin. A *cis*-geometry leads to the formation of the *E*-configured double bond. In general, the Grob fragmentation is the most commonly employed method for the synthesis of cyclononenes due to the predictability of the stereochemical outcome of the product. The construction of cyclononenes can furthermore be achieved by thermal [3,3]-sigmatropic rearrangements of 1,5-dienes **C**. When the reaction proceeds via a chairlike transition state, the substituents are oriented with minimal steric hindrance to give the *E*,*E*-configured nine-

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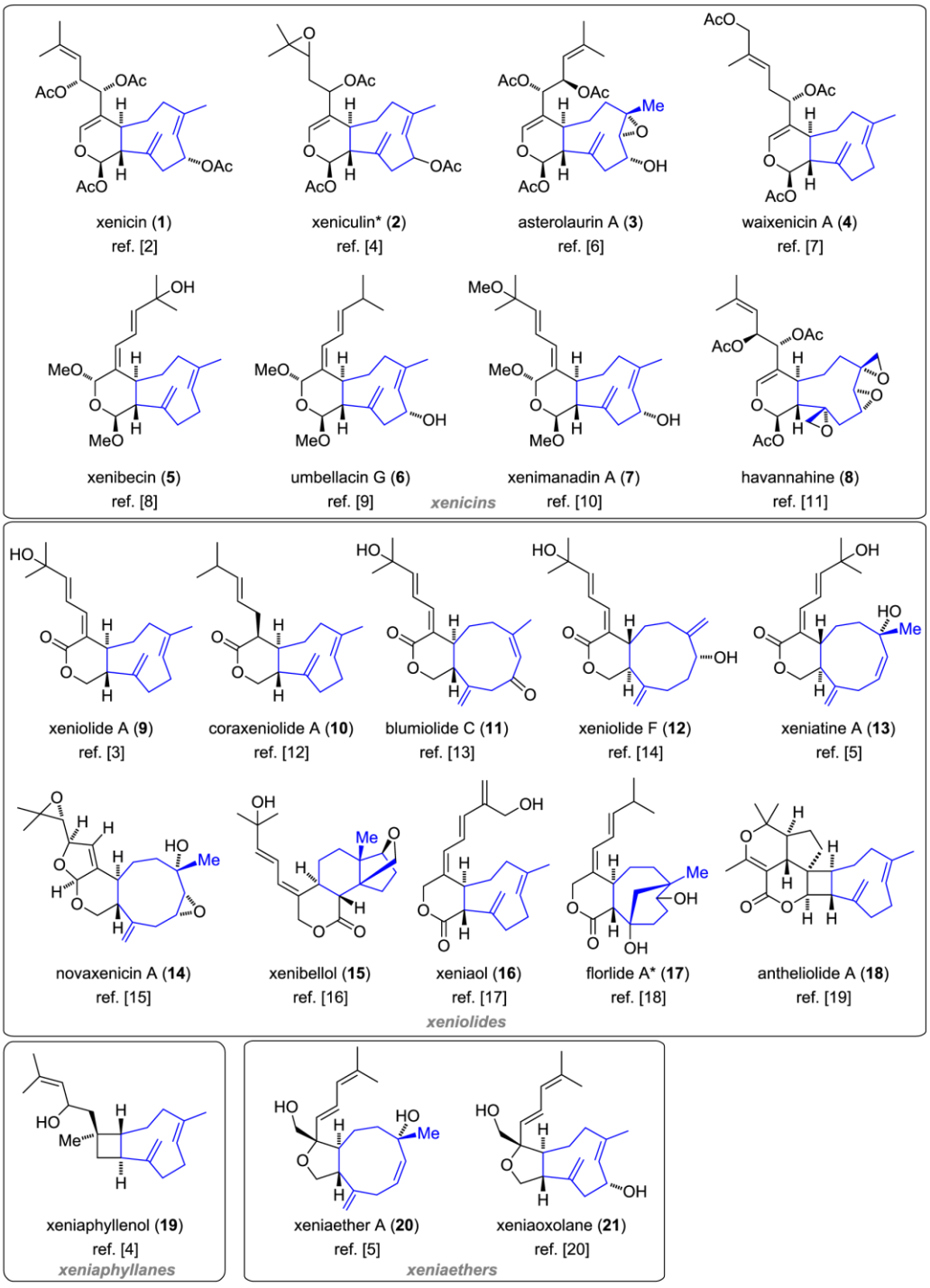

Figure 2: Overview of selected Xenia diterpenoids according to the four subclasses [2-20]. The nine-membered carbocyclic rings are highlighted in blue. *Stereochemistry not determined.

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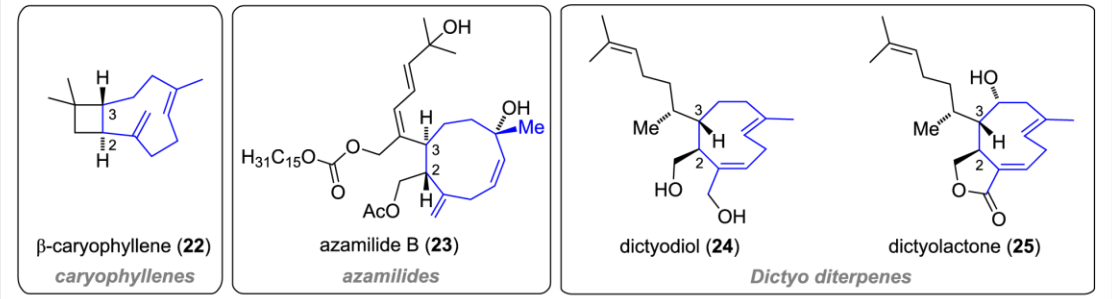
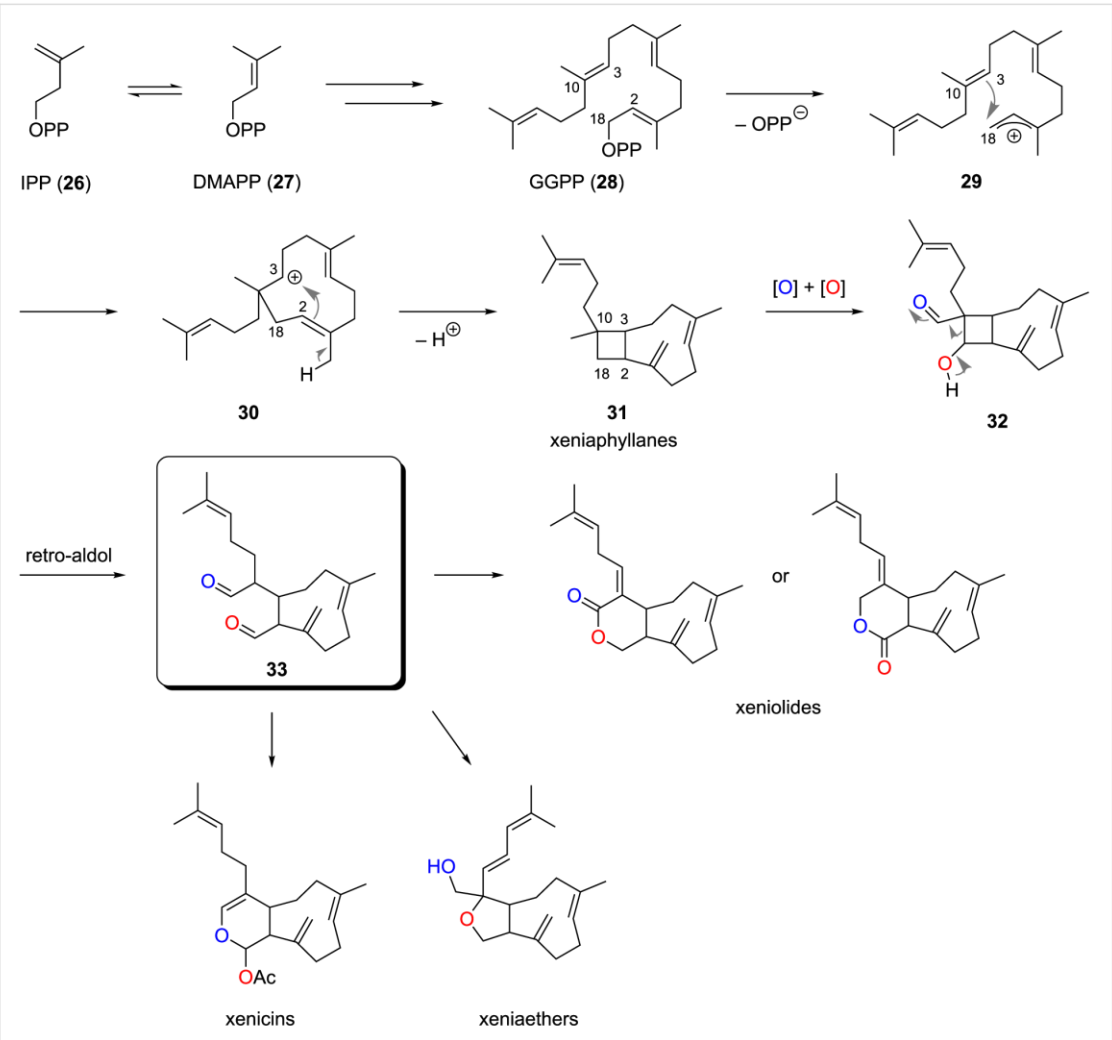


Figure 3: Representative members of the caryophyllenes, azamilides and *Dictyota* diterpenes.



Scheme 1: Proposed biosynthesis of *Xenia* diterpenoids (OPP = pyrophosphate, GGPP = geranylgeranyl pyrophosphate, IPP = isoprenyl pyrophosphate, DMAPP = dimethylallyl pyrophosphate).

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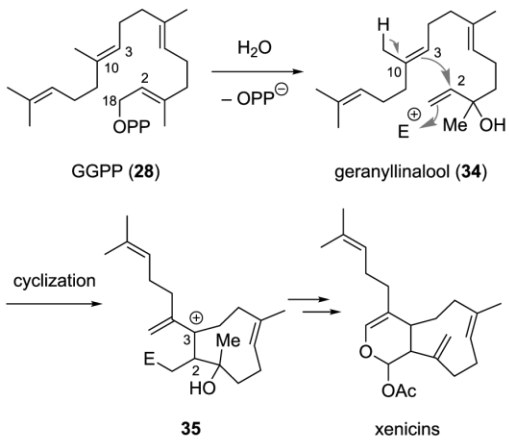
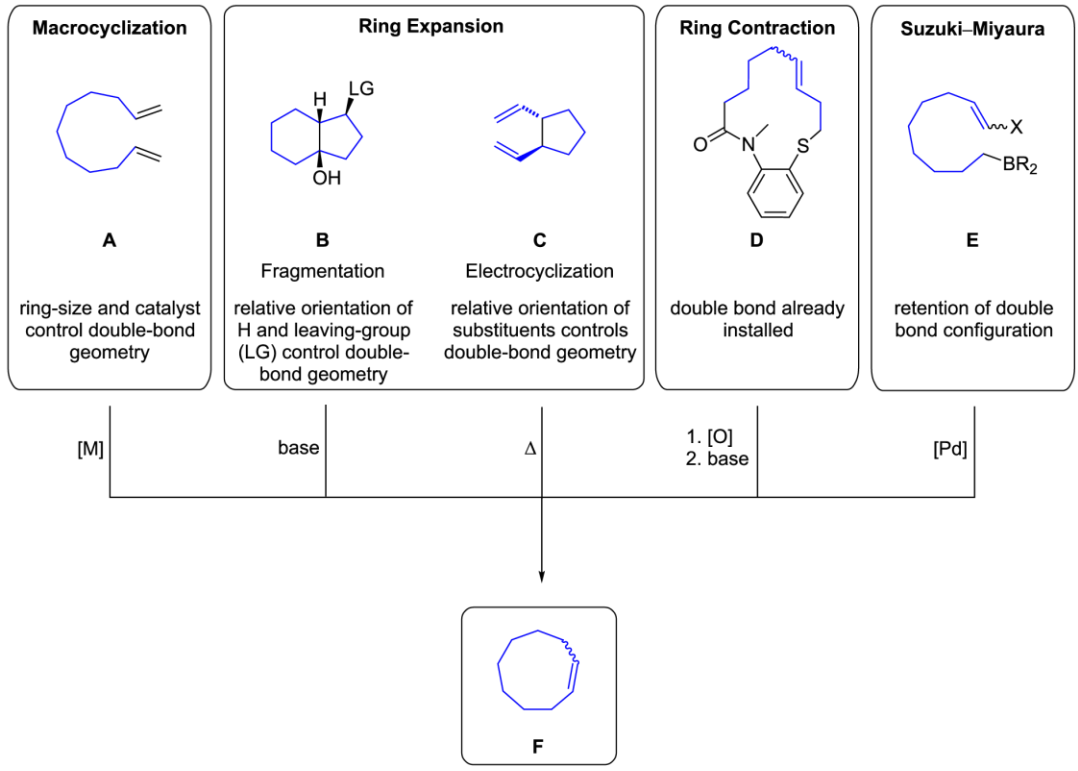


Scheme 2: Direct synthesis of the nine-membered carbocycle as proposed by Schmitz and van der Helm (E = electrophilic oxygen species) [2].

membered ring. Ring contraction reactions of 13-membered lactams afford cyclononenes via intramolecular acyl transfer reactions. The configuration of the double bond derives from precursor **D** and thus allows the formation of *E*- or *Z*-configured cyclononenes. Additionally, the intramolecular palladium-catalyzed cyclization of haloalkenes with organoboranes affords cyclononenes with retention of the double bond configuration [28]. The corresponding allylic alcohols can be prepared by a Nozaki–Hiyama–Kishi coupling of haloalkenes with aldehydes.

The first synthesis of the unusual nine-membered carbocyclic ring was reported by Corey for the total synthesis of β-caryophyllene in 1963 (Scheme 4) [29-31]. Starting with a photochemical [2 + 2] cycloaddition between 2-cyclohexen-1-one (**37**) and isobutene (**36**), an isomeric mixture of *trans*- and *cis*-fused [4.2.0]octanone was obtained (*trans*-**38**/*cis*-**39** = 4:1). The more stable *cis*-bicycle **39** could be obtained by isomerization of *trans*-**38** with base. Acylation with sodium hydride and dimethyl carbonate followed by methylation furnished β-keto ester **40**. Addition of lithium acetylide **41** to the keto group led to acetal **42**. Hydrogenation of the triple bond under basic



Scheme 3: The construction of *E*- or *Z*-cyclononenes.

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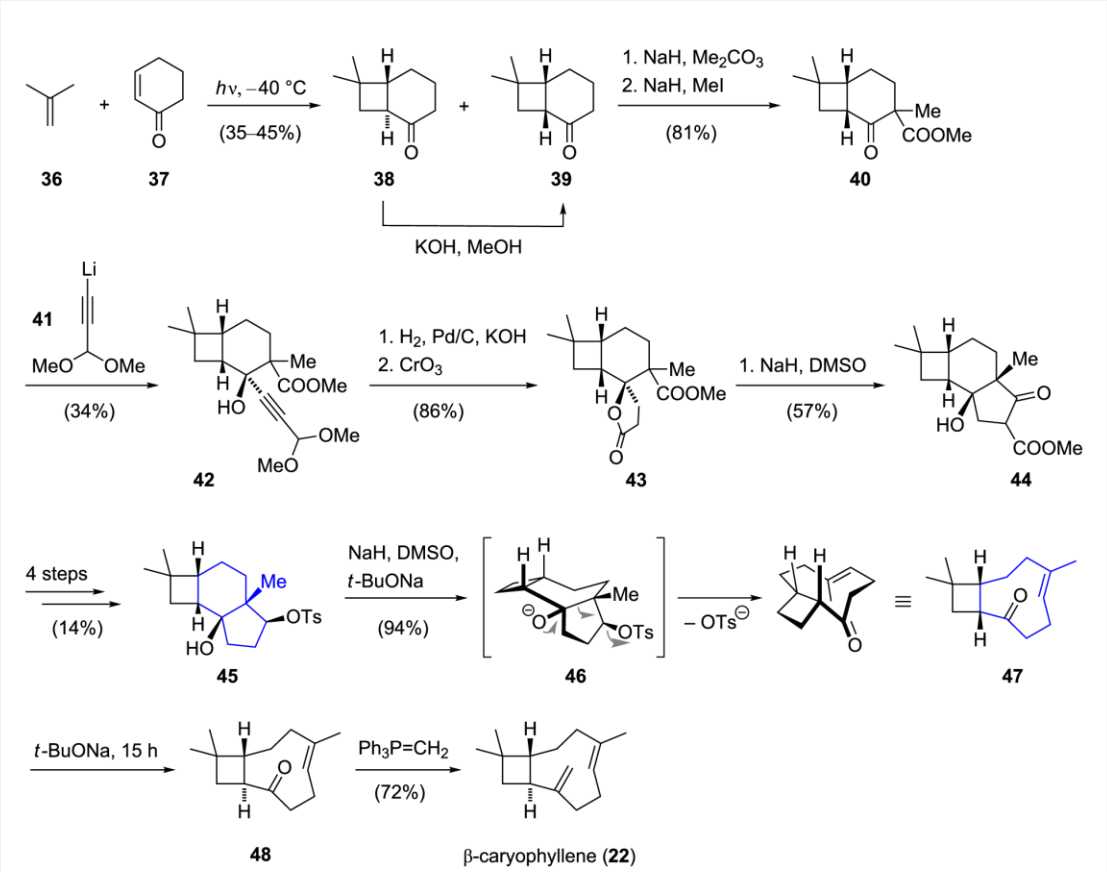

Scheme 4: Total synthesis of racemic β-caryophyllene (**22**) by Corey.

conditions resulted in cleavage of the acetal and ring closure to the corresponding lactol which was oxidized with chromic acid to furnish γ-lactone **43**. An ensuing Dieckmann condensation [32] of **43** afforded a 4,6,5-tricycle which was converted to the fragmentation precursor **45** in four further steps. A base-mediated Wharton-type Grob fragmentation [33] then served as the key step to construct the cyclononene motif of bicycle **47**. Prolonged exposure of the resulting *cis*-fused 4,9-bicycle **47** to sodium *tert*-butoxide gave rise to the epimerized *trans*-isomer **48**. Finally, the exocyclic double bond was introduced by olefination of ketone **48** and thus completed the racemic total synthesis of β-caryophyllene (**22**) in 13 steps. This elegant synthesis received considerable attention and revealed already at that time the great potential of modern synthetic organic chemistry.

More than 20 years later, in 1984, Oishi and co-workers reported a different strategy which culminated in the total synthesis of racemic β-caryophyllene (**22**) (Scheme 5) [34]. Their synthesis commenced with conjugate addition of ethyl (phenylsulfonyl)acetate, a methylsulfonyl anion equivalent, to cyclobutene ester **49** followed by a sequence consisting of saponification, regioselective decarboxylation and reesterification to afford methyl ester **50**. The ester group was reduced with lithium aluminum hydride and the resulting alcohol was converted to the corresponding silyl ether. Next, alkylation of the metalated sulfone with allylic chloride **51** afforded alcohol **52** after desilylation. Subsequent desulfonylation with sodium amalgam and Jones oxidation of the primary alcohol furnished carboxylic acid **53**. The corresponding tertiary amide was then formed by sequential reaction of carboxylic acid **53** with oxalyl chloride and *N*-methylaniline derivative **54**. The following two-step debenzylation sequence afforded alcohol **55** which was converted to the corresponding mesylate, serving as a key intermediate for the construction of the nine-membered carbocyclic ring. Treatment of this intermediate with potassium *tert*-

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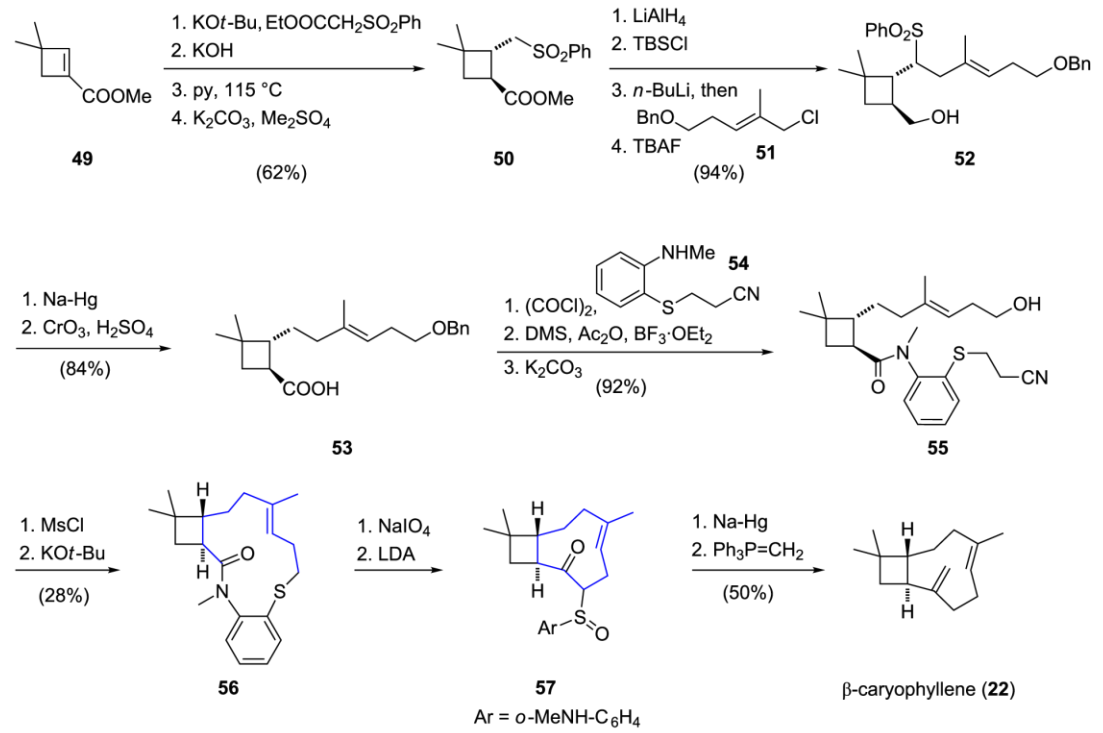

Scheme 5: Total synthesis of racemic β-caryophyllene (**22**) by Oishi.

butoxide led to the cleavage of the 2-cyanoethylsulfide moiety and the generation of a thiolate anion, which underwent S_N2 displacement of the primary mesylate, affording the 13-membered lactam **56**. The stage was now set for the key intramolecular acyl transfer reaction to form the cyclononene motif. After sodium periodate oxidation of sulfide **56** to the corresponding sulfoxide, addition of lithium diisopropylamide initiated the intramolecular acyl transfer and led to formation of cyclononene **57** in quantitative yield. Reductive desulfonylation and a final Wittig olefination of the ketone then afforded racemic β-caryophyllene (**22**). In summary, the total synthesis of β-caryophyllene was achieved in 19 steps with an overall yield of 6.3%. Although the key intramolecular acyl transfer reaction for construction of the cyclononene ring could be realized in quantitative yield, the low-yielding formation of the macrocyclic thioether reduced the overall efficiency of the presented synthetic route. Based on a similar strategy and using the corresponding *Z*-isomer of cyclization precursor **39**, Oishi and co-workers reported a total synthesis of racemic isocaryophyllene, the *cis* double bond isomer of caryophyllene. Further total syntheses of isocaryophyllene have also been reported by Kumar [35,36], Miller [37] and Bertrand [38].

In 1995, Pfander reported the synthesis of an important building block [24] for the total synthesis of coraxeniolide A (**10**) [12], starting from chiral (−)-Hajos–Parrish diketone (**58**) [39]. Based on Pfander's seminal work, the first total synthesis of a xenicane diterpenoid was then accomplished by Leumann in 2000 (Scheme 6) [40]. Starting from enantiopure (−)-Hajos–Parrish diketone (**58**), allylic alcohol **59** was prepared by regioselective reduction of the carbonyl group, silylation of the resulting alcohol and further reduction of the enone moiety. An ensuing transetherification of alcohol **59** with ethyl vinyl ether gave an allyl vinyl ether, which underwent a magnesium perchlorate-promoted [1,3]-sigmatropic rearrangement [41] to afford an aldehyde that was converted to dimethylacetal **60**. The following epoxidation proceeded with good stereoselectivity (α/β ≈ 11:1) and the regioselective opening of the epoxide moiety using lithium cyanide afforded a β-hydroxy nitrile in a *trans*-diaxial arrangement. Under basic conditions, the configuration of the nitrile group at C2 was inverted, furnishing the thermodynamically more stable **61**. Nitrile **61** was then converted to lactol **62** in seven further steps. Next, the cyclononene ring of **63** was constructed via a Grob fragmentation of 6,6,5-tricycle **62**, affording the bicyclic product **63** in very good yield,

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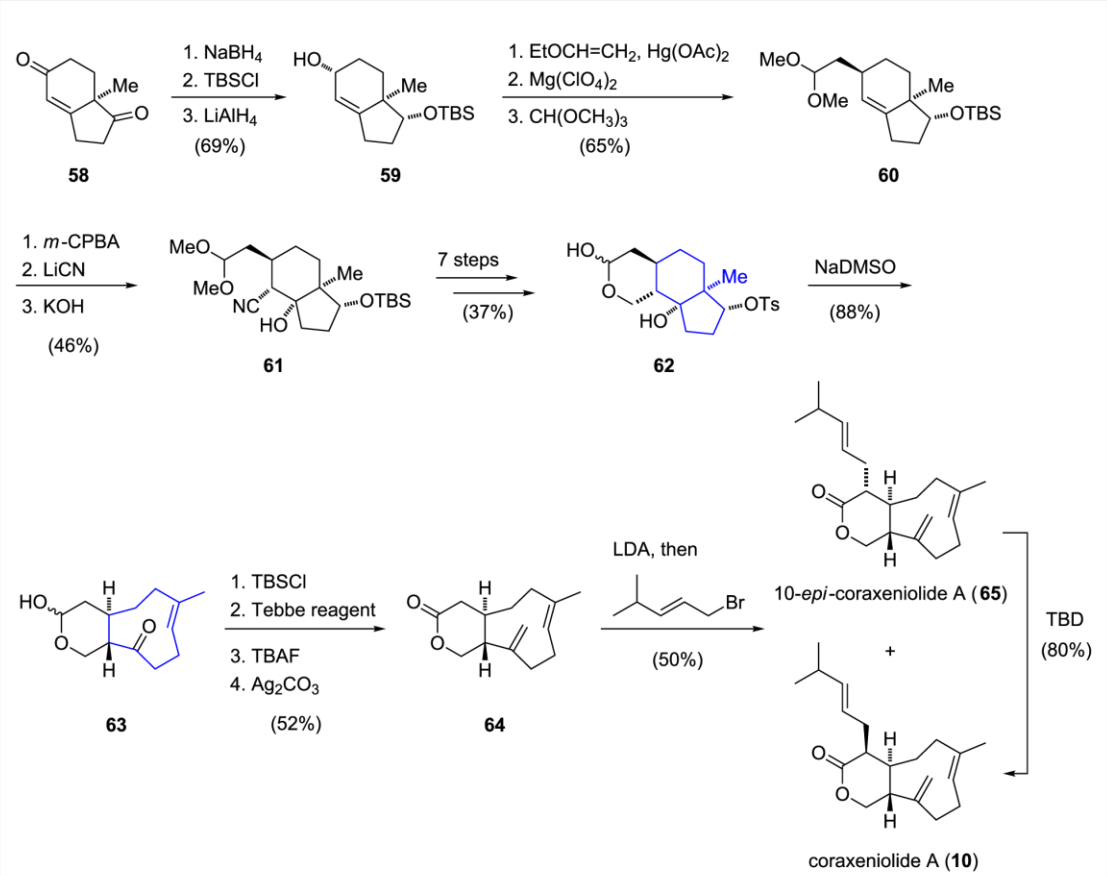

Scheme 6: Total synthesis of coraxeniolide A (**10**) by Leumann.

however, as a mixture of lactol epimers (α/β ≈ 56:44). Silyl protection of the lactol and subsequent Tebbe olefination [42] of the ketone group installed the exocyclic double bond of the nine-membered carbocycle. Desilylation followed by oxidation with silver carbonate then afforded lactone **64**. For the introduction of the side chain, the enolate derived from lactone **64** was treated with 1-bromo-4-methylpent-2-ene, giving a 1:6 mixture of coraxeniolide A (**10**) and its epimer **65**. By equilibration with triazabicyclodecene (TBD), the ratio of **10**:**65** could be inverted to 3:1. In summary, coraxeniolide A (**10**) was synthesized in a longest linear sequence of 23 steps with an overall yield of 1.4%.

The most complex xenicane diterpenoid synthesized to date is pentacyclic antheliolide A (**18**) [18] by Corey (Scheme 7) [43]. The linear precursor **68** was prepared from vinyl bromide **66** and aldehyde **67** in six steps in 34% yield. After saponification of the ester functionality, treatment with tosyl chloride and trimethylamine resulted in the formation of a ketene that underwent a diastereoselective intramolecular [2 + 2] cycloaddition to provide bicyclic ketone **69**. Addition of TMS cerium acetylide to the carbonyl group of **69**, followed by desilylation under basic conditions gave rise to (±)-ethynylcarbinol, which was separated by chiral HPLC. The desired diastereomer was then transformed to benzene sulfinate ester **70**. A palladium-catalyzed [2,3]-sigmatropic rearrangement formed an isomeric allenic sulfone [44] which, upon conjugate addition of diethyl amine followed by hydrolysis afforded a β-ketosulfone. For the following ring closure, the primary alcohol was desilylated and converted to the corresponding allylic carbonate **71**. The cyclononene structure **72** was then assembled via a palladium-catalyzed and base-mediated cyclization of carbonate **71** [45]. Reductive cleavage of the sulfone using aluminium amalgam afforded a ketone, which was converted to an exocyclic double bond by treatment with Tebbe's reagent [42]. In order to convert the methoxy acetal to the corresponding lactone,

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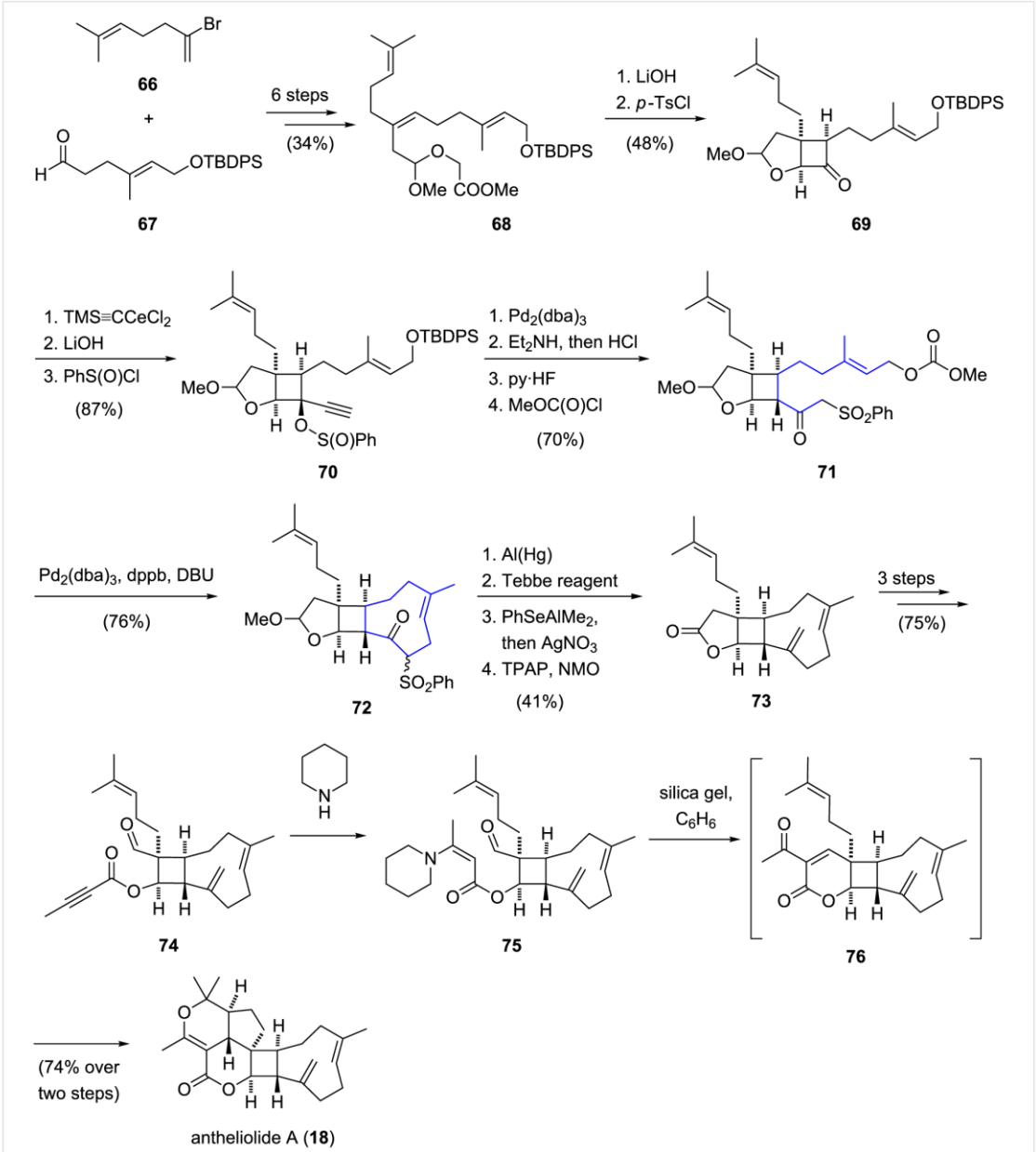

Scheme 7: Total synthesis of antheliolide A (**18**) by Corey.

without affecting the sensitive caryophyllene-like subunit, the methoxy group was replaced with a phenylseleno moiety, which was converted to the alcohol and finally oxidized to lactone **73**. In three further steps, lactone **73** was converted to aldehyde ester **74**, which upon treatment with piperidine gave a β-enamino ester **75**. Finally, an elegant cascade reaction involving an aldol condensation, followed by a hetereo Diels–Alder reaction closed the last three rings and antheliolide A (**18**) was obtained in 74% yield. In summary, the successful total synthesis of antheliolide A proceeded in 25 linear steps with an overall yield of 1.7%.

The total syntheses of coraxeniolide A (**10**) and β-caryophyllene (**22**) reported by Corey [46] in 2008 are based on Pfander's

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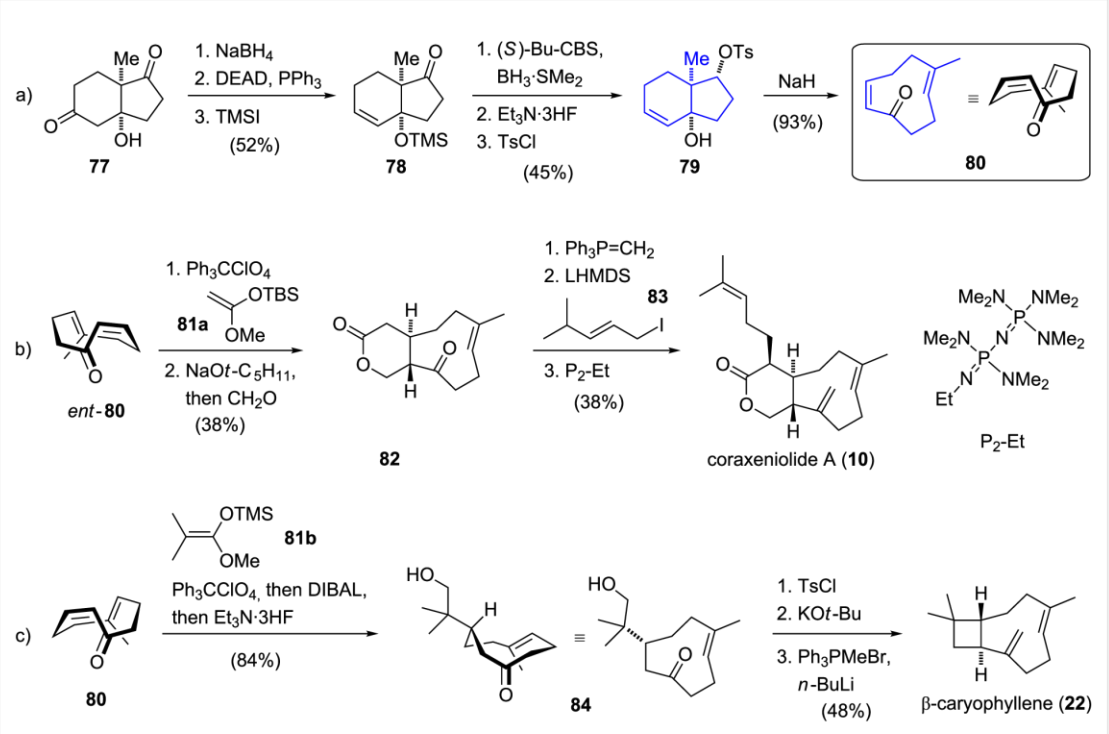
idea [24] to construct the cyclononene fragment from (−)-Hajos–Parrish diketone (**58**) [39] (Scheme 8). Chiral hydroxy dione **77** was synthesized according to a literature-known procedure [47]. Regioselective reduction with sodium borohydride, followed by dehydration under Mitsunobu conditions and silylation of the tertiary alcohol furnished trimethylsiloxy ketone **78**. The ketone functionality was then diastereoselectively reduced under Corey–Bakshi–Shibata conditions [48] and an ensuing desilylation furnished a diol. In order to introduce a leaving group for the following key step, the secondary hydroxy group was tosylated to afford **79**. Once again, a stereospecific Grob fragmentation of tosylate **79** served as the key step for the synthesis of the enantiomerically pure and configurationally stable nine-membered *E*,*Z*-dienone **80**. The synthesis of the enantiomer of dienone **80**, *ent*-**80**, was accomplished by a route parallel to that presented in Scheme 8a, starting from *ent*-**77**. The highly efficient construction of these versatile intermediates provides a basis to synthesize a variety of natural products containing this macrocyclic structural motif. Based on chiral enone **80** and its enantiomer, *ent*-**80**, coraxeniolide A (**10**) and β-caryophyllene (**22**) were synthesized in five and four further steps, respectively. The synthesis of **10** continued with a trityl perchlorate-catalyzed conjugate addition of silyl ketene acetal **81a** to enone *ent*-**80**. Deprotonation and trapping of the resulting enolate with formaldehyde furnished lactone **82** in a regio- and stereoselective fashion. Introduction of the exocyclic double bond proved to be challenging and therefore salt-free, highly reactive methylenetriphenylphosphorane was used. Finally, α-alkylation of the lactone with iodide **83** provided coraxeniolide A (**10**) and its epimer in a 1:6 ratio which could be reversed to 4:1 by base-mediated equilibration. Purification by column chromatography, allowed the two epimers to be separated and afforded coraxeniolide A (**10**) in 38% yield over three steps.

Additionally, the enantioselective total synthesis of β-caryophyllene was realized starting from key intermediate **80**. The route commenced with conjugate addition of silyl ketene acetal **81b** to enone **80** from the sterically less hindered re-face. The ester group was selectively reduced and desilylation afforded alcohol **84**. The generated primary alcohol was tosylated and regioselective deprotonation followed by intramolecular α-alkylation stereoselectively formed the cyclobutane ring. A final Wittig methylenation introduced the exocyclic double bond and afforded (−)-β-caryophyllene (**22**), for the first time in an enantioselective manner. In conclusion, Corey's protocol for



Scheme 8: a) Synthesis of enantiomer **80**, b) total syntheses of coraxeniolide A (**10**) and c) β-caryophyllene (**22**) by Corey.

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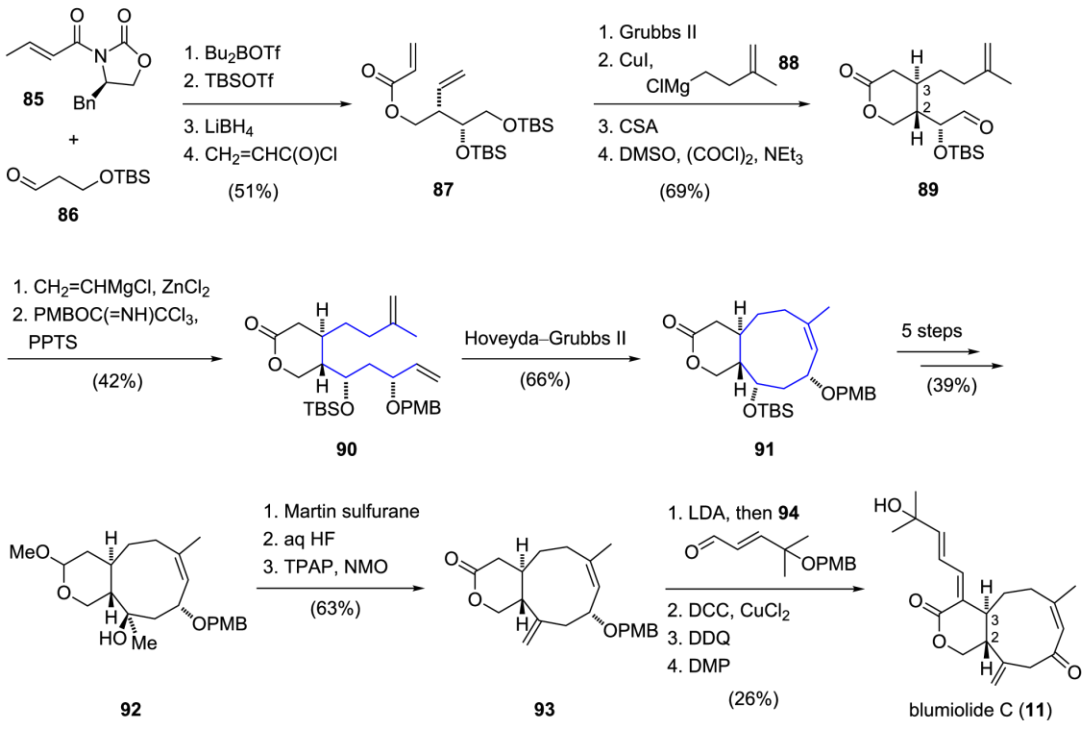
the synthesis of a highly versatile building block represents a valuable platform for the construction of many different metabolites containing the nine-membered carbocyclic ring segment. The application of this useful intermediate was elegantly demonstrated in the synthesis of coraxeniolide A proceeding in 14% yield over five steps.

Altmann and co-workers disclosed the total synthesis of blumiolide C (**11**) [20] employing a *Z*-selective ring-closing metathesis reaction for construction of the cyclononene unit [49]. The synthesis started with a diastereoselective Evans syn-aldol reaction between substituted propanal **86** and *E*-crotonyl-oxazolidinone **85** (Scheme 9). The resulting secondary alcohol was silylated and the chiral auxiliary was cleaved with lithium borohydride. Acylation with acryloyl chloride gave ester **87** and a ring-closing metathesis reaction using Grubbs second generation catalyst [50] furnished an α,β-unsaturated lactone. Subsequent 1,4-addition of the cuprate derived from alkylmagnesium chloride **88** provided the *trans*-product with excellent diastereoselectivity and thus installed the required stereocenter at the C3 position of the natural product. After deprotection of the sterically less hindered silyl ether, the resultant primary alcohol was oxidized to give aldehyde **89**. By treatment with in situ generated divinylzinc, aldehyde **89** was transformed to an allylic alcohol which was converted to the corresponding *para*-methoxybenzyl ether **90** using Bundle's reagent [51]. In the key step of the synthesis, the nine-membered carbocyclic ring was constructed via a ring-closing metathesis reaction. Under optimized conditions, Hoveyda–Grubbs second generation catalyst [52] selectively converted diene **90** to the bicyclic ring system **91** in 66% yield. For the installation of the exocyclic double bond, bicycle **92** was treated with Martin sulfurane [53]. Subsequent hydrolysis of the acetal functionality and oxidation of the resulting lactol restored the lactone function in bicycle **93**. The side chain of blumiolide C was introduced by an aldol reaction between lactone **93** and aldehyde **94**. In the final sequence, blumiolide C (**11**) was obtained via stereospecific dehydration, removal of the *para*-methoxybenzyl ether and oxidation. In summary, the total synthesis of blumiolide C was accomplished in an overall yield of 0.63%.

In 2005, Hiersemann and co-workers reported an approach towards the synthesis of xeniolide F [13] employing a catalytic asymmetric Claisen rearrangement to set the crucial stereocen-



Scheme 9: Total synthesis of blumiolide C (**11**) by Altmann.

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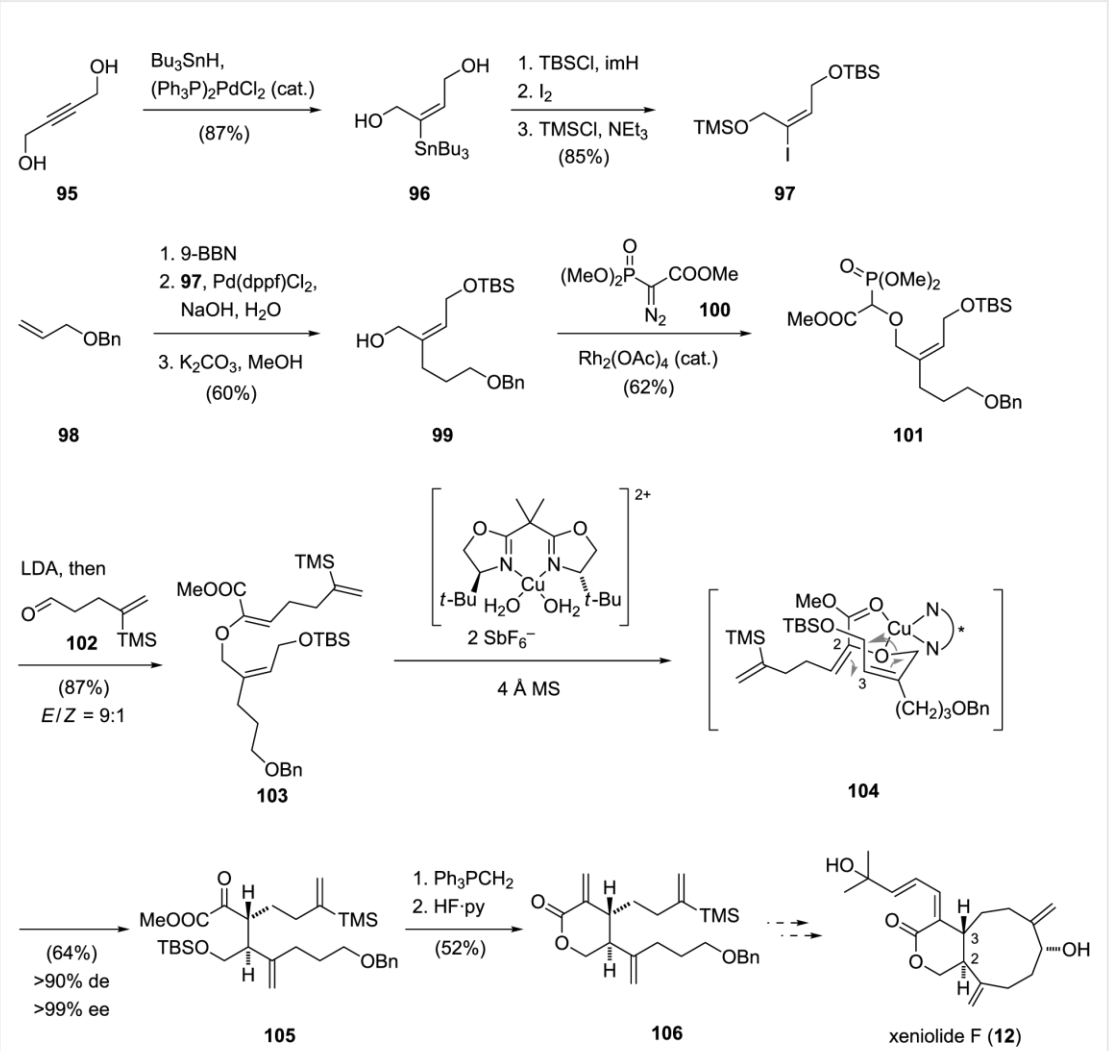
ters at the C2 and C3 positions (Scheme 10) [54]. The synthesis commenced with the preparation of diol **96** by a palladium-catalyzed hydrostannylation of 2-butyne-1,4-diol (**95**). Regioselective silylation with *tert*-butyldimethylsilyl chloride of the sterically less hindered alcohol, iodination and silylation of the primary alcohol with trimethylsilyl chloride gave vinyl iodide **97**. The following palladium-catalyzed B-alkyl Suzuki–Miyaura cross coupling between the borane derived from alkene **98** and vinyl iodide **97** furnished a *Z*-configured alkene. Deprotection of the trimethylsilyl ether then afforded alcohol **99**. A rhodium(II)-catalyzed O–H insertion reaction of the rhodium carbenoid derived from diazophosphonoacetate **100** and alcohol **99** afforded intermediate **101** which was treated with lithium diisopropylamide and aldehyde **102** to afford alkene **103** with high *E*-selectivity. The following asymmetric copper(II)-catalyzed Claisen rearrangement [55], which is postulated to proceed via the chair-like transition state **104**, afforded key intermediate **105** with high diastereo- and enantioselectivity. Preparation of the δ-lactone **106** of the A ring of xeniolide F was then realized by treatment of Claisen product **105** with the methylene Wittig reagent, followed by desilylation and lactonization. Although a successful synthetic approach leading to lactone **106** was thus established, further efforts to complete the total synthesis of xeniolide F (**12**) have yet to be reported.



Scheme 10: Synthesis of a xeniolide F precursor by Hiersemann.

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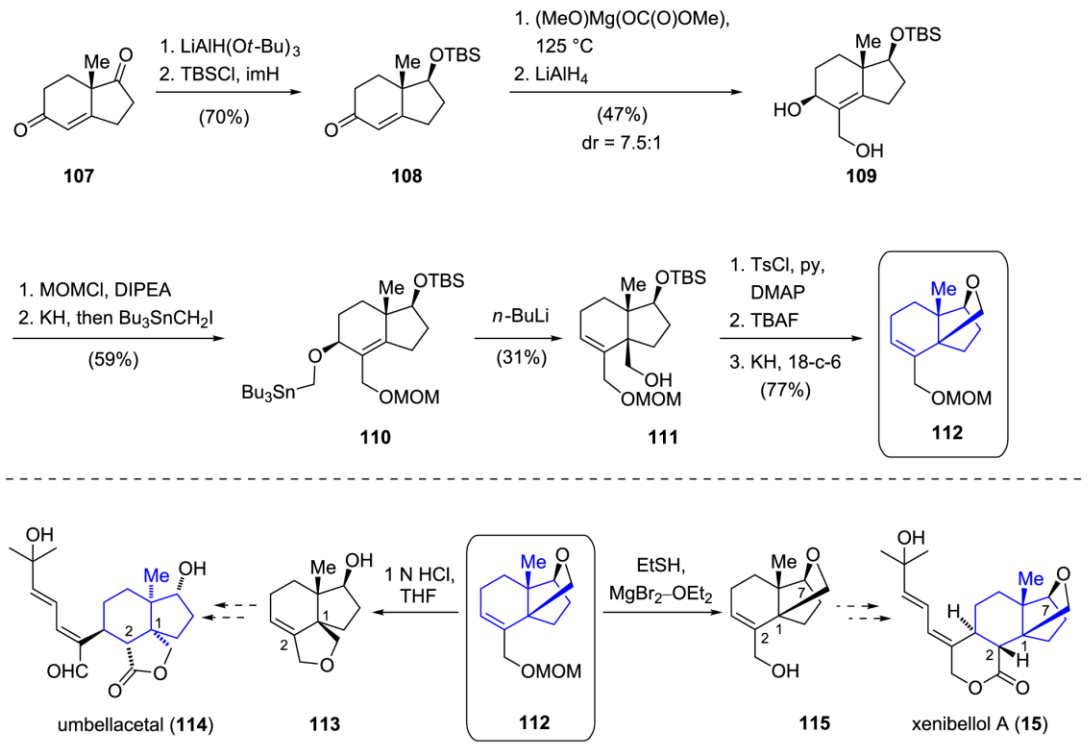
Efforts aimed at constructing the core structure of xenibellol A (**15**) [15] and umbellacetal (**114**) [56] employing a 2,3-Wittig–Still rearrangement as the key step were reported by Danishefsky and co-workers (Scheme 11) [57]. In contrast to other xenicanes mentioned above, xenibellol A (**15**) does not possess the characteristic nine-membered carbocyclic ring but rather features a 6,5,5-ring system, containing an unusual oxolane bridge between C1 and C7. Hajos–Parrish diketone (**107**) [39] served as the starting material for the preparation of key intermediate **112**. Selective reduction of the ketone and silylation of the resulting alcohol furnished enone **108**. α-Carboxylation of the enone with magnesium methyl carbonate and a global reduction of the carbonyl functionalities afforded allylic alcohol **109**. The precursor for the key reaction was obtained by formation of the methoxymethyl (MOM) ether from primary alcohol **109** and subsequent conversion of the allylic alcohol to stannane **110**. The following 2,3-Wittig–Still rearrangement [58] employing *n*-butyllithium afforded primary alcohol **111** in 31% yield and enabled the installation of the C1 quaternary stereocenter. According to the authors, a competing 1,2-Wittig rearrangement and reduction pathway posed a significant challenge in this transformation. Desilylation and regioselective tosylation of the primary alcohol **111** set the stage for the construction of the oxolane via Williamson etherification, which was realized by treatment with potassium hydride. Surprisingly, the following deprotection of the MOM ether using standard reaction conditions (1 N aqueous hydrochloric acid) led to opening of the oxolane ring and afforded tricycle **113** which features the carbon framework of structurally related umbellacetal (**114**). Gratifyingly, when magnesium bromide and ethanethiol were used as a mild alternative for the cleavage of the MOM ether, the xenibellol core could be obtained. Although the key 2,3-Wittig–Still rearrangement proceeded in low yield and further improvements are necessary, a promising route towards the synthesis of umbellacetal (**114**) and xenibellol (**15**) was thus established.

Yao and co-workers have investigated a synthetic approach towards the soft coral metabolite plumisclerin A by Pauson–Khand annulation and SmI_2-mediated radical cyclization [59]. The xenicane-related diterpenoid (isolated from the same marine organism as xenicin **116**) possesses a complex ring



Scheme 11: Synthesis of the xenibellol (**15**) and the umbellacetal (**114**) core by Danishefsky.

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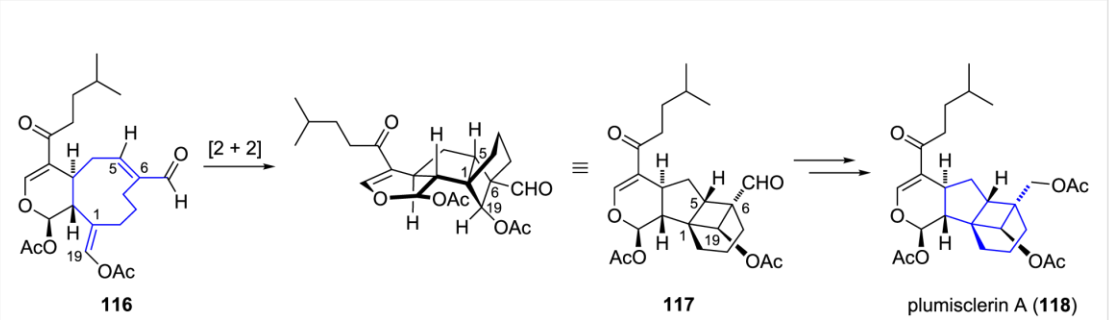
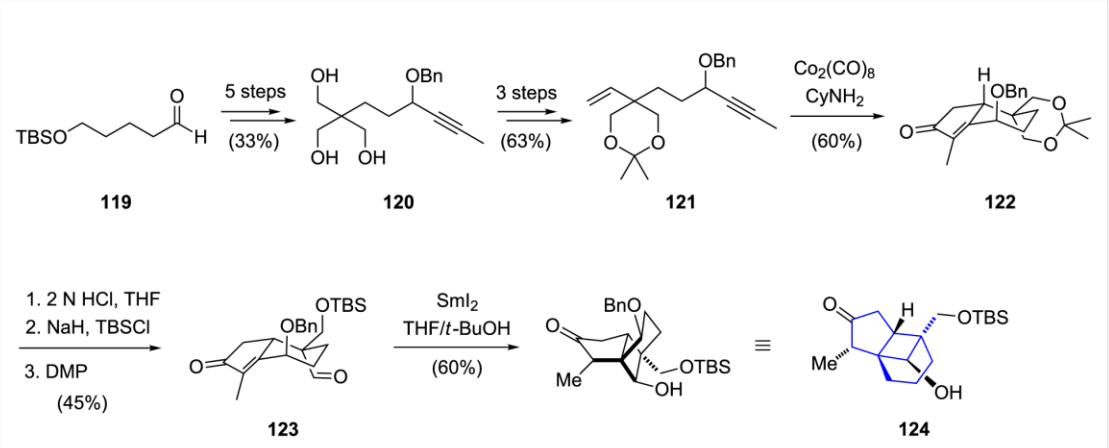
system that is proposed to be biosynthetically derived from the xenicin diterpenoid **116** by an intramolecular [2 + 2] cycloaddition (Scheme 12) [60].

The synthetic route commenced with known aldehyde **119** which was converted to triol **120** in five steps (Scheme 13). The introduction of the benzyl ether next to the alkyne moiety was necessary to control the stereochemical outcome of the key annulation, and further three steps enabled preparation of the annulation precursor **121**. The following Pauson–Khand reaction [61] for the construction of the fused bicyclic structure **122** was performed by treatment of **121** with dicobaltoctacarbonyl in the presence of cyclohexylamine. Hydrolysis of the acetonide, chemoselective silylation and oxidation afforded aldehyde **123**. Next, the formation of the cyclobutanol ring was realized by an intramolecular samarium diiodide-mediated radical conjugate addition to afford tricycle **124** in 60% yield. Introduction of the dihydropyran ring of plumisclerin A (**118**) was envisioned to be carried out at a late stage of the synthesis, but efforts towards its construction have yet to be reported.

In 2009, the enantioselective total synthesis of 4-hydroxydictyolactone (**137**) was reported by Williams and co-workers (Scheme 14) [62]. Starting from α,β-unsaturated ester **125**, allylic alcohol **126** was synthesized in four steps. Esterification with (*R*)-(+)-citronellic acid (**127**) yielded a single diastereomer of ester **128**. Addition of lithium diisopropylamide to a mixture of **128**, trimethylsilyl chloride and triethylamine initiated an Ireland–Claisen rearrangement [63] which gave carboxylic acid **129** in 85% yield and with high diastereoselectivity (dr = 94:6). Carboxylic acid **129** was then converted to intermediate **130** in seven further steps. An intramolecular coupling between the formate ester and the allylic bromide provided lactol **131** in excellent stereoselectivity (dr > 95:5). The preparation of sec-



Scheme 12: Proposed biosynthesis of plumisclerin A (**118**).



Scheme 13: Synthesis of the tricyclic core structure of plumisclerin A by Yao.

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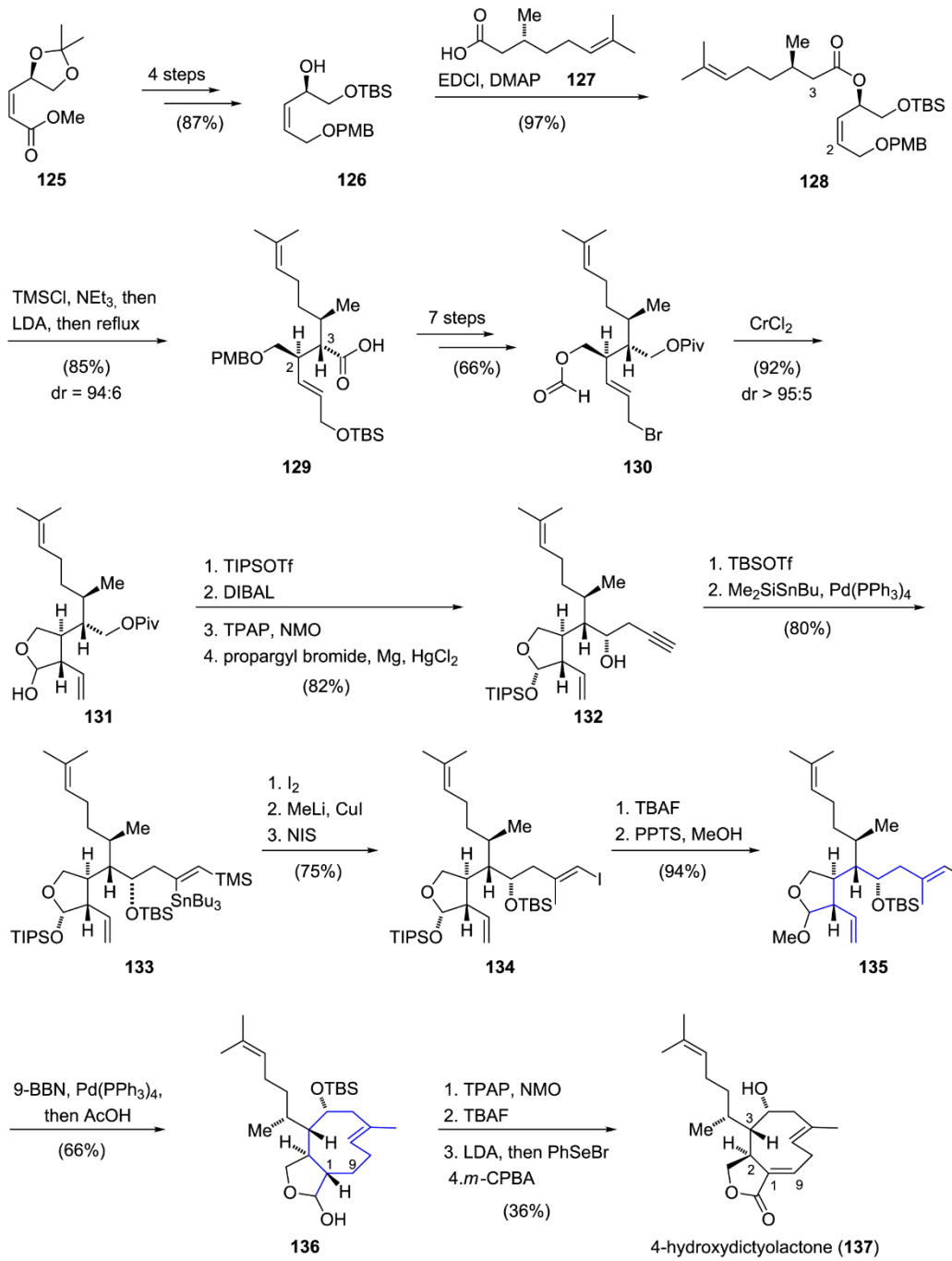

Scheme 14: Total synthesis of 4-hydroxydictyolactone (**137**) by Williams.

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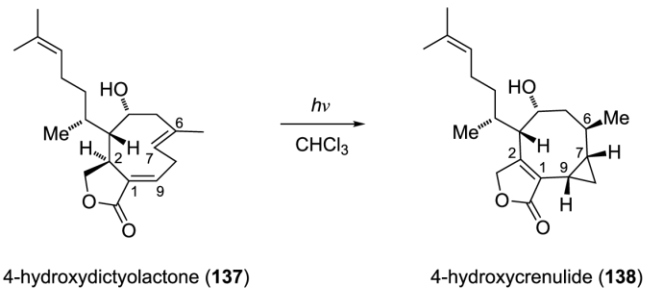
ondary alcohol **132** was accomplished by cleavage of the pivaloate ester, oxidation under Ley–Griffith oxidation [64] and subsequent addition of propargylmagnesium bromide. *O*-Silylation of the propargylic alcohol followed by a regioselective palladium-catalyzed *syn*-silylstannylation yielded product **133**. After employing a three-step protocol for the sequential replacement of the stannyl and silyl substituents, *E*-vinyl iodide **134** was obtained with retention of the olefin geometry. The following intramolecular key coupling step between the vinyl iodide and the terminal alkene for the formation of the nine-membered carbocycle was realized via a B-alkyl Suzuki–Miyaura cross-coupling reaction. Optimization studies of this key ring closure with different protecting groups on the lactol functionality revealed methyl acetal **135** as the most efficient substrate for this transformation. The challenging key step was finally realized in 66% yield and gave, after hydrolysis of the acetal with acetic acid, a mixture of *trans*-fused diastereomers **136**. Finally, a sequence consisting of oxidation, deprotection of the silyl ether and selenoxide elimination introduced the C1,C9 double bond to furnish 4-hydroxydictyolactone (**137**). In summary, the total synthesis of 4-hydroxydictyolactone was successfully completed in 30 linear steps with an overall yield of 4.8%.

Paquette and co-workers disclosed the enantioselective total synthesis of the *Xenia* diterpenoid related crenulatane (+)-acetoxycrenulide (**151**) [65-67]. The skeleton of crenulatanes, which features an eight-membered carbocyclic ring fused to a cyclopropane ring, may be the product of a photoisomerization of xenicanes. This hypothesis was further supported by the fact that crenulatanes usually co-occur with xenicanes in brown seaweeds of the family *Dictyotaceae*. Evidence for this proposed biogenetic origin of crenulatanes has been provided by Guella and Pietra who showed that irradiation of 4-hydroxydictyolactone (**137**) with ultraviolet light (254 nm) led to the formation of 4-hydroxycrenulide (**138**) (Scheme 15) [68]. Although this transformation remains mechanistically unclear, the authors suggested that either a free radical process or a photoinduced double bond isomerization (C9,C1 to C1,C2) followed by an [1,3]H shift might lead to the formation of 4-hydroxycrenulide (**138**).

The total synthesis of (+)-acetoxycrenulide (**151**) commenced with preparation of butenolide **140** from (*R*)-citronellol (**139**) in an 11-step sequence. Next, the two stereocenters at C2 and C3 position were installed by stereoselective conjugate addition of enantiopure α-allylphosphonamide **141** to butenolide **140**. After cleavage of the chiral auxiliary by ozonolysis, aldehyde **142** was protected as the dimethoxy acetal and reduction of the lactone followed by olefination furnished alkene **143**. The lactone fragment of the natural product was then installed by acidic hydrolysis of the acetal functionality and subsequent oxidation gave γ-lactone **144**. Ozonolysis of the terminal alkene and addition of (phenylseleno)methyllithium to the resulting aldehyde afforded secondary alcohol **145**. Temporary protection of the alcohol followed by an aldol reaction of the lactone with *E*-crotonaldehyde led to an inseparable mixture (dr = 1:1) of β-hydroxy lactone **146**. The synthesis of the key precursor for formation of the cyclooctene core was achieved via an acid-catalyzed cyclization to form tetrahydropyran **147**. The following key sequence consisted of a thermal selenoxide 1,2-elimination to generate allyl vinyl ether **148** which underwent a stereoselective Claisen rearrangement [69] to furnish cyclooctenone **149** in 55% yield. A highly stereoselective Simmons–Smith reaction [70] delivered the cyclopropyl ring exclusively from the accessible α-face to give **150**. The synthesis of (+)-acetoxycrenulide (**151**) was completed in seven further steps and in summary proceeded in 33 steps (longest linear sequence) and in 1% overall yield (Scheme 16).

In addition to the presented strategies for the synthesis of *Xenia* diterpenoids, total syntheses of the *Xenia* sesquiterpenes xenitorin B and C were also reported [71].



4-hydroxydictyolactone (**137**) 4-hydroxycrenulide (**138**)

Scheme 15: Photoisomerization of 4-hydroxydictyolactone (**137**) to 4-hydroxycrenulide (**138**).

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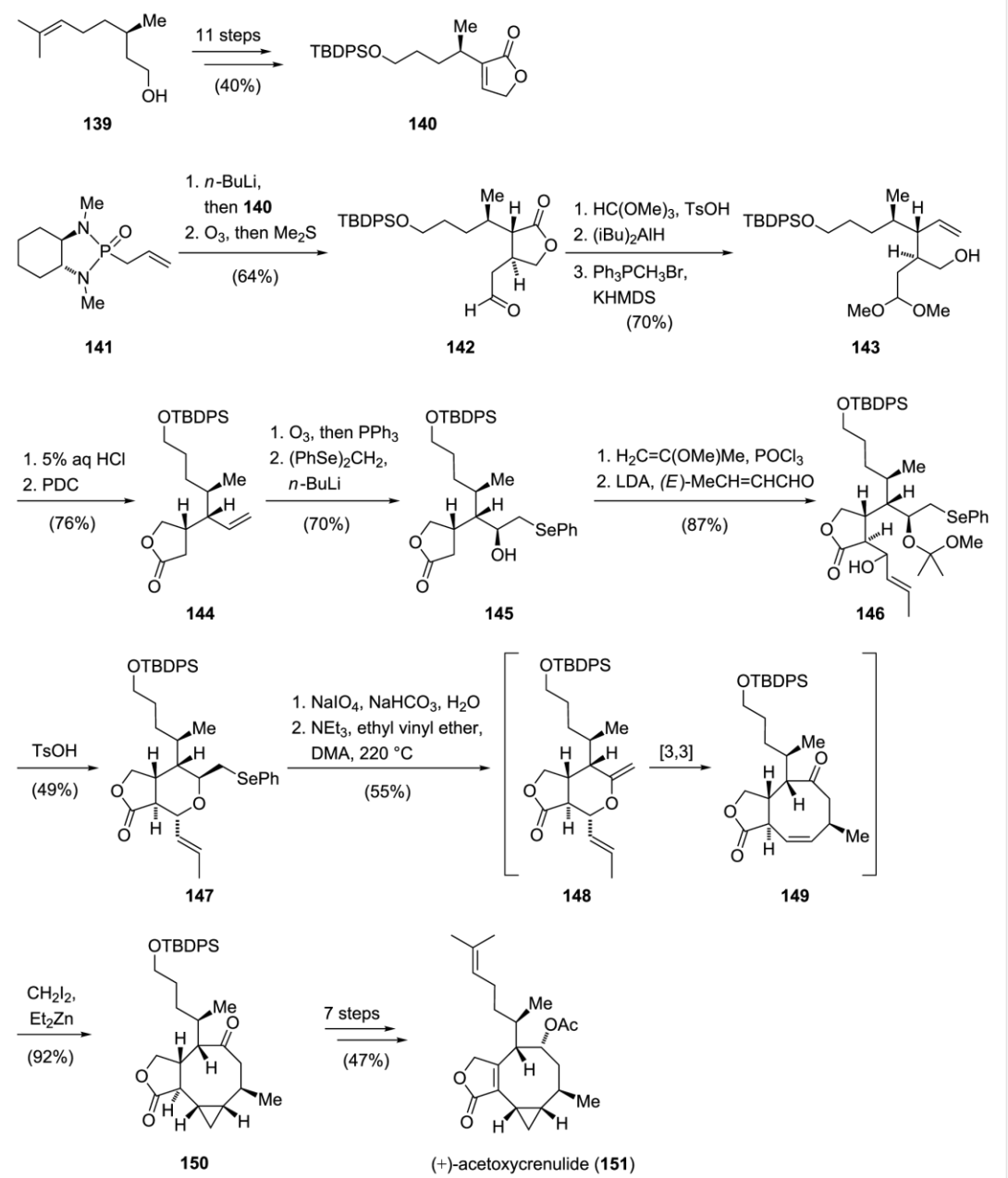

Scheme 16: The total synthesis of (+)-acetoxycrenulide (**151**) by Paquette.

Conclusion

This review has presented various synthetic approaches towards xenicane and xenicane-related diterpenoids. Additionally, total syntheses of xeniolides and of a crenulatane natural product were illustrated. It has been shown that the rare structural features of *Xenia* diterpenoids represent an enduring challenge for the total synthesis of these fascinating metabolites. For these reasons, several strategies for the preparation of the characteristic nine-membered carbocyclic ring structures have been developed. The synthetic strategies are typically based on ring

expansion (Grob-type fragmentation and sigmatropic rearrangements), ring closing (metathesis and transition metal-catalyzed coupling) and ring contracting reactions. The choice of tactic is dependent on the individual substitution pattern of the target compound. However, many of the presented strategies rely on long synthetic sequences that cannot provide large amounts of synthetic material which is required for further investigations of the biological activity of these natural products, and ultimately for drug discovery. The development of short and efficient synthetic routes towards xenicane natural products therefore remains a great challenge of this exciting research field.

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2 Project Outline

2.1 Waixenicin A – Isolation and Bioactivity

Waixenicin A (**11**) is a xenicane diterpenoid that was isolated in 1984 from the octocoral *Anthelia edmondsoni* (family *Xeniidae*), collected on Hawaiian shores.[26] Isolation of the natural product was carried out by hexane extraction of the freeze-dried organism, followed by extraction with methanol and purification with reversed phase HPLC to give waixenicin A (**11**) in 0.17% yield. Waixenicin B (**12**), which differs from waixenicin A (**11**) by oxygenation at C9,[‡] was also isolated from *Anthelia edmondsoni* and its structure has been further proven by single crystal X-ray analysis[§] (Figure 4).[26] The natural product belongs to the xenicine subfamily and contains the characteristic (*E*)-cyclononene framework found in most members of the xenicane family of natural products. The nine-membered ring is *trans*-fused to a dihydropyran ring.

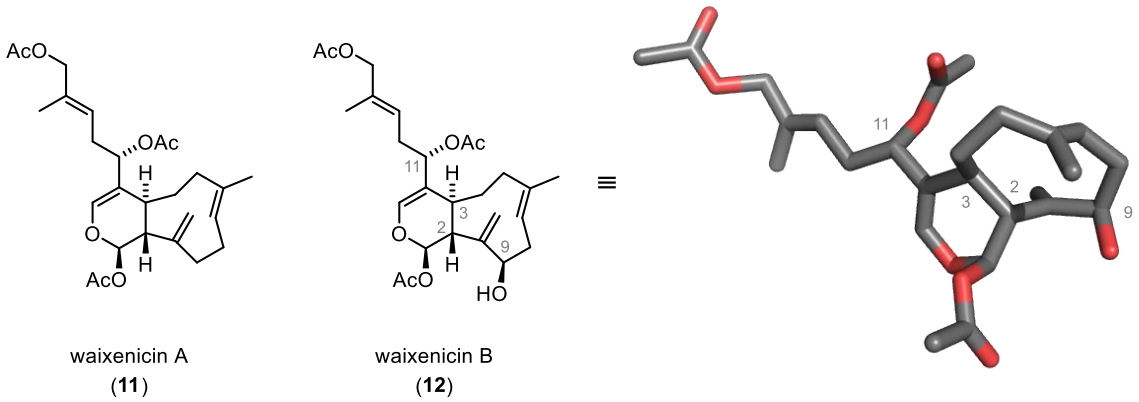


Figure 4. The two xenicins waixenicin A (**11**) and waixenicin B (**12**), and the molecular structure of waixenicin B (**12**). Hydrogen atoms are omitted for clarity and no absolute configuration is implied.

Waixenicin A (**11**) was found to have an inhibitory effect on the growth and proliferation of cells. Its cytotoxicity originates from the strong and specific inhibition of transient receptor potential melastatin 7 (TRPM7) channels.[27–29] TRPM7 is a protein that contains both an ion channel and an intrinsic kinase domain. These channels mediate the influx of divalent metal cations (especially Mg^{2+}) into the cytosol and are thus involved in cellular and systemic Mg^{2+} homeostasis.[30] In recent years, waixenicin A (**11**) has become a useful pharmacological tool to study the function of TRPM7 channels. The inhibitory effect of the natural product on TRPM7 was found to be highly dependent on the intracellular Mg^{2+} concentration. Furthermore, it was found that inhibition of TRPM7 receptors caused a cell cycle arrest in the G_0/G_1 phase in cancer cells.[27]

[‡] The common numbering of the xenicane skeleton, introduced by Schmitz and van der Helm in: *J. Am. Chem. Soc.* **1977,** *99*, 5780–5784, is used throughout this thesis (except for the Experimental Part).
[§] CCDC deposition number 1132300 contains the supplementary crystallographic data for waixenicin B (**12**). The data can be obtained from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/

These properties identified TRPM7 channels as promising targets for the suppression of cancer (especially breast and gastric cancer), but also for the treatment of neurological, immunological and cardiovascular diseases.

The investigations of the inhibitory effect of waixenicin A (**11**) on TRPM7 channels were carried out with small amounts of the secondary metabolite isolated from natural sources. For further investigations, especially regarding the use of this natural product as a potential anti-cancer agent, the development of a reliable synthetic route is required. It was therefore the goal of this Ph.D. thesis to develop a convergent and modular synthesis of waixenicin A (**11**).

2.2 Aims of the Project

Waixenicin A (**11**) represents a unique and challenging target for total synthesis and no completed synthesis for this natural product has been reported to date. The primary challenge lies in the successful incorporation of the (*E*)-cyclononene fragment. Additionally, the *trans*-fused dihydropyran motif was expected to cause difficulties in its preparation. The low degree of functionalization of the nine-membered carbocycle also limits the possible retrosynthetic disconnections. From a synthetic point of view, the main task of a synthesis of waixenicin A (**11**) is therefore the construction of the 6,9-bicyclic core structure. We planned to access waixenicin A (**11**) by two different strategies (Figure 5). At first, we aimed to synthesize the core structure with a Grob fragmentation approach by disconnection of bond C1−C6 (disconnection “a”), relying on established methodology for the synthesis of (*E*)-cyclononenes (Figure 5, left). In addition, we set out to investigate the direct cyclization of the nine-membered carbocycle from acyclic precursors by disconnection of bond C4−C5 (disconnection “b”) (Figure 5, right).

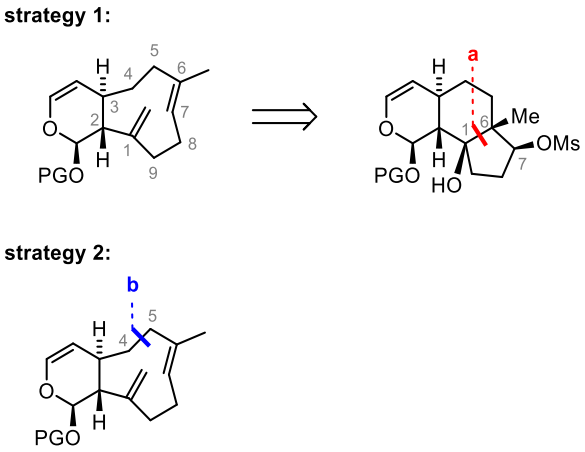
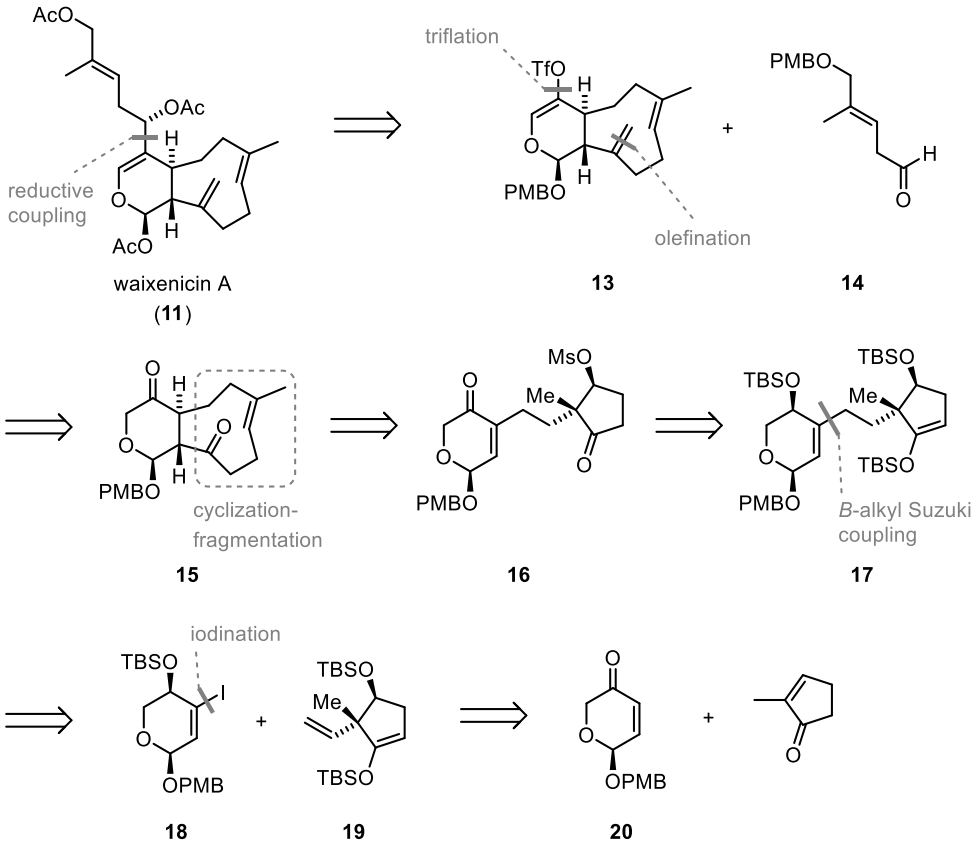


Figure 5. Retrosynthetic bond disconnections for the 6,9-bicyclic core structure of waixenicin A (**11**) (PG = protecting group).

3 Results and Discussion

3.1 First-generation Approach: SmI_2-mediated Grob Fragmentation

Medium-sized carbocycles consist of eight to eleven carbon atoms and have the largest ring strain compared to the most prevalent five- or six-membered rings, and large rings, containing more than eleven carbon atoms. The main sources of this ring strain are transannular interactions between hydrogen atoms pointing into the ring. Ring expansion or fragmentation reactions[31–36] have often been utilized in the past to access substituted medium-sized rings and are the best way to overcome the entropic and enthalpic factors[37] associated with their formation. The initial approach for the synthesis of waixenicin A (**11**) was based on a fragmentation reaction to construct the (*E*)-cyclononene fragment. Our retrosynthetic analysis is depicted in Scheme 2.

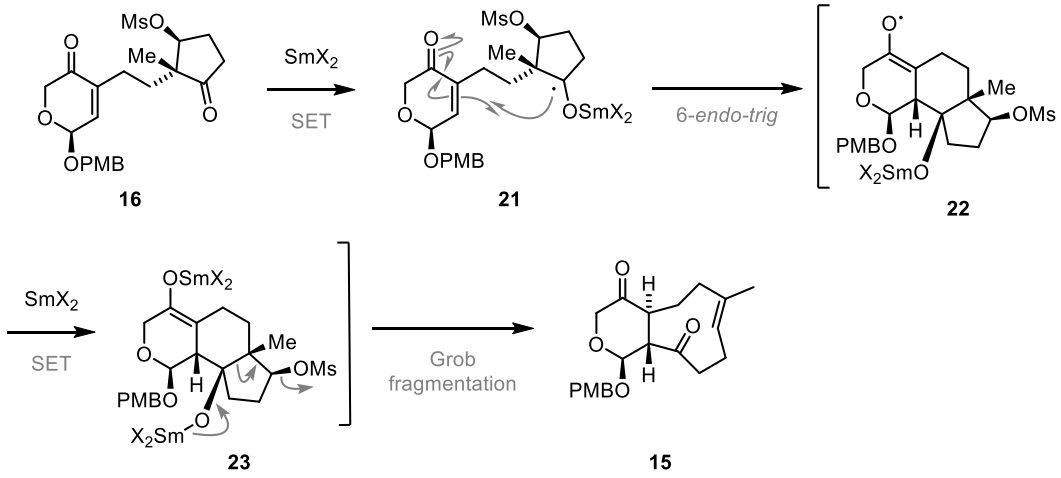


Scheme 2. Initial retrosynthetic analysis of waixenicin A (**11**).

Literature-known aldehyde **14**[38] and triflate **13** should be reductively coupled to introduce the side chain of the natural product **11**. The exocyclic double bond of the cyclononene should be introduced via olefination. The characteristic (*E*)-cyclononene fragment was intended to be constructed by a unique samarium dihalide-mediated radical cyclization-fragmentation cascade of enone **16**. Our plans for the preparation of this cyclization precursor were based on a *B*-alkyl Suzuki cross coupling between alkene **19** and vinyl iodide **18**. These two building blocks were in turn envisioned to be

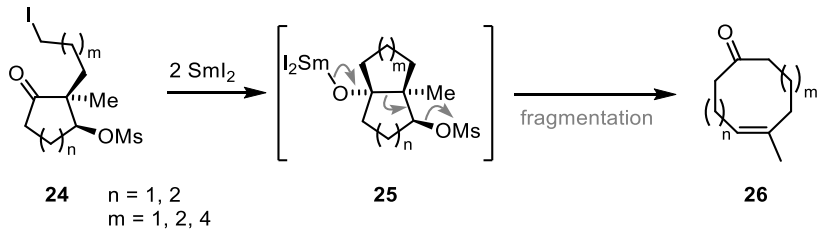
derived from literature-known chiral enone **20**[39] and commercially available 2-methyl-2-cyclopenten-1-one.

The sequential radical cyclization-fragmentation reaction for the construction of the (*E*)-cyclononene motif is further illustrated in Scheme 3. The cascade should be initiated by a samarium dihalide-mediated single-electron transfer (SET) to afford ketyl radical **21**, which should attack the enone moiety in a 6-*endo-trig* cyclization mode to give intermediate **22**. Addition of an additional equivalent of samarium dihalide should then generate samarium(III) alkoxide **23**, which should undergo a stereospecific Grob fragmentation[40–42] to afford the nine-membered ring. The synperiplanar orientation between the methyl group and the mesylate should establish the (*E*)-configuration of the trisubstituted C–C double bond.



Scheme 3. The cyclization-fragmentation cascade for the construction of the (*E*)-cyclononene fragment.

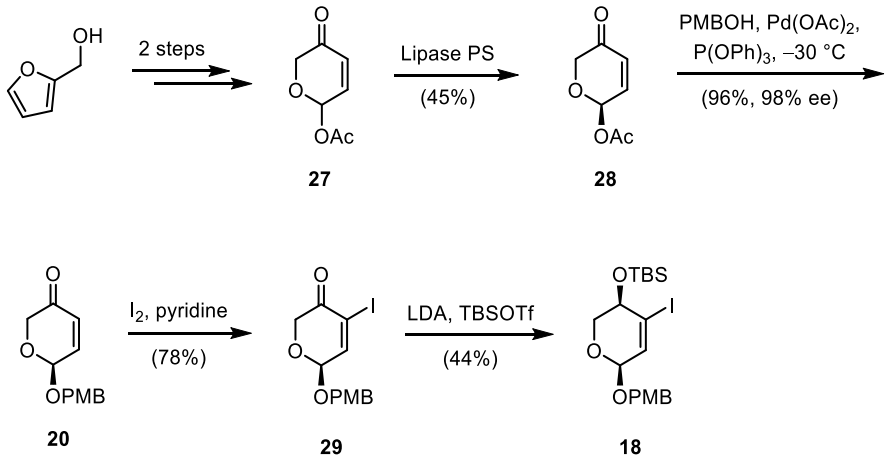
Our retrosynthetic analysis was inspired by Molander's work where eight-, nine- and ten-membered rings were accessed by a SmI_2-mediated cyclization-fragmentation cascade of simple iodocycloalkanones.[43] In this domino reaction, a bicyclic system was first formed, which then fragmented to afford the carbocycles (**24**→**26**) (Scheme 4).



Scheme 4. Molander's SmI_2-mediated cyclization-fragmentation cascade for the synthesis of medium-sized rings.

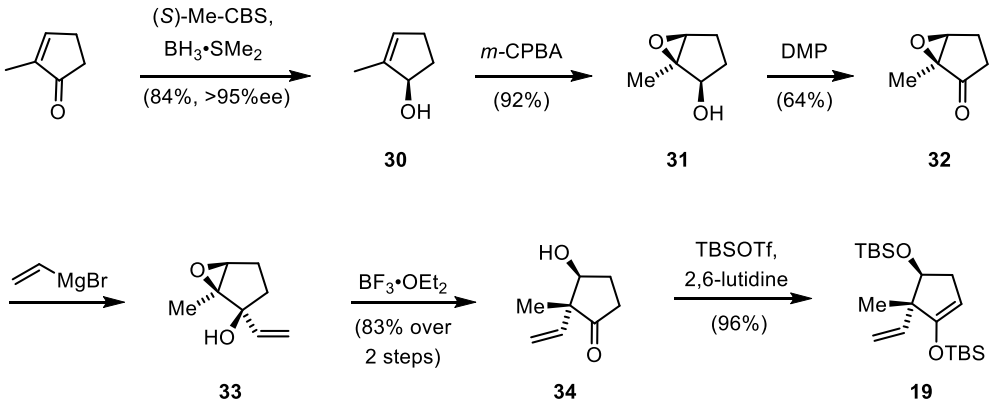
Our synthetic route commenced with the preparation of vinyl iodide **18** in six steps from commercially available furfuryl alcohol.[44] The introduction of the stereocenter was achieved via

enzymatic resolution by treatment of racemic acetal **27** with immobilized lipase PS.[45] The synthesis of enantiopure *para*-methoxybenzyl (PMB) protected enone **20** was accomplished using Feringa's procedure for stereospecific palladium-catalyzed acetal formation.[39] Treatment of enone **20** with iodine and pyridine afforded α-iodo enone **29**. The following reduction was achieved using the nitrogen analog of the Meerwein–Ponndorf–Verley reduction.[46] Thus, reaction of α-iodo enone **29** with lithium diisopropylamide (LDA) and subsequent trapping of the generated alkoxide with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) afforded vinyl iodide **18** (Scheme 5).



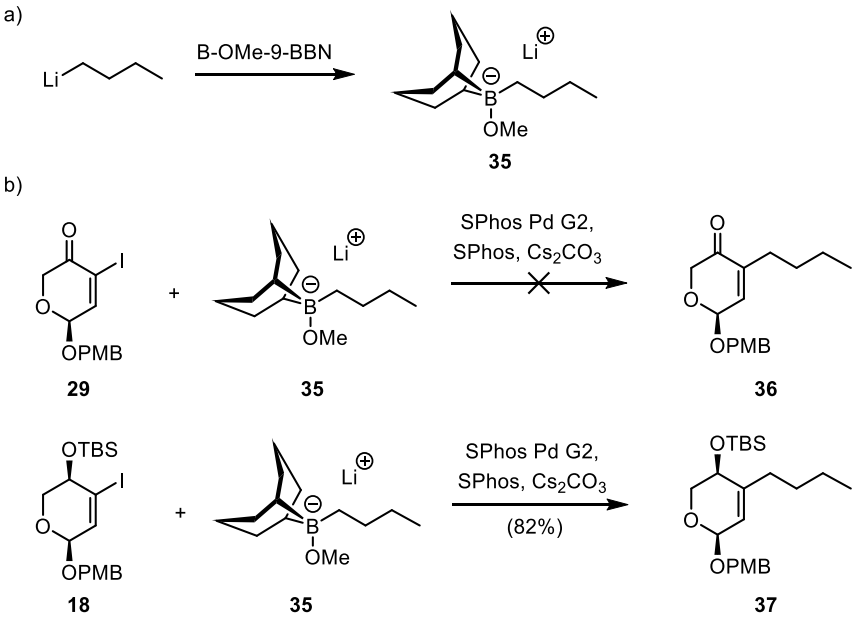
Scheme 5. Synthesis of vinyl iodide **18** from furfuryl alcohol.

For the synthesis of building block **19**, the first step was the preparation of enantiomerically pure allylic alcohol **30** (Scheme 6). This task was realized by the enantioselective reduction of commercially available 2-methyl-2-cyclopenten-1-one with stoichiometric amounts of borane-dimethyl sulfide complex and (*S*)-methyl-CBS-oxazaborolidine at 0 °C. The enantiomeric excess of alcohol **30** (95% ee) was determined by ^{19}F NMR analysis of the two diastereomeric Mosher's ester derivatives.[47] Hydroxy-directed epoxidation of **30** with *meta*-chloroperbenzoic acid (*m*-CPBA) provided epoxy alcohol **31** in good yield. Oxidation of the alcohol with Dess–Martin periodinane (DMP)[48] afforded epoxyketone **32** and subsequent addition of vinyl magnesium bromide resulted in the formation of allylic alcohol **33** as a single diastereomer. The following semi-pinacol rearrangement[49] proceeded in high yields using borane trifluoride-etherate as Lewis acid to furnish ketone **34**. In summary, the synthesis of chiral building block **34** has been accomplished in five steps starting from 2-methyl-2-cyclopenten-1-one with an overall yield of 41%. Treatment of intermediate **34** with TBSOTf in the presence of 2,6-lutidine afforded the TBS enol ether **19**.



Scheme 6. Enantioselective synthesis of building block **19**.

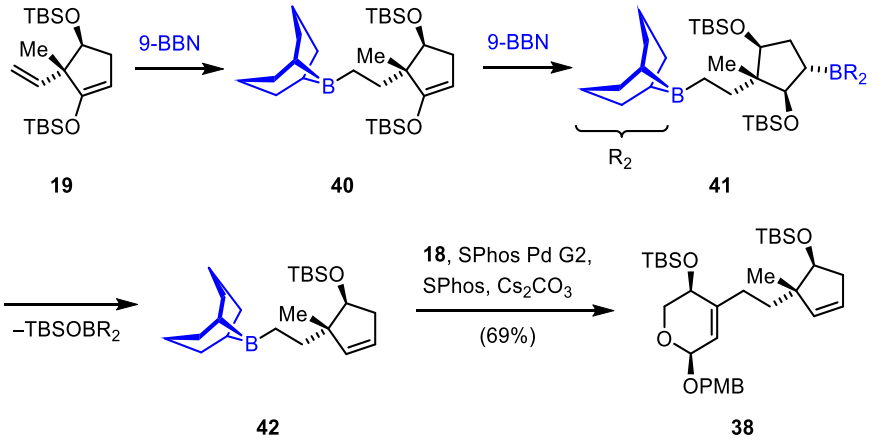
With the requisite coupling partners in hand, efforts toward the fragment coupling were undertaken (Scheme 7). As a guide, we considered previous studies on the transmetalation of alkyllithium species with *B*-methoxy-9-BBN, followed by a Suzuki–Miyaura cross coupling using Buchwald's SPhos ligand and SPhos second generation precatalyst.[50] In initial studies, the corresponding lithium boronate **35** was used as a model boronate to examine the feasibility of the coupling with α-iodo enone **29** or vinyl iodide **18**. It was found that the reaction of α-iodo enone **29** with *in situ* generated boronate **35** resulted in complete decomposition of **29**. However, the coupling of vinyl iodide **18** with intermediate boronate **35** occurred smoothly at 50 °C within two hours using 5 mol% of the catalyst to give the coupled product **37** in good yield.



Scheme 7. (a) *In situ* preparation of boronate **35** from *n*-butyl lithium and B-OMe-9-BBN. (b) Suzuki–Miyaura cross coupling coupling of iodides **29** and **18** with boronate **35**.

Motivated by this result, alkene **19** was first converted to the corresponding organoborane species **40** by treatment with two equivalents of 9-BBN (THF, 60 °C), which was then submitted to vinyl

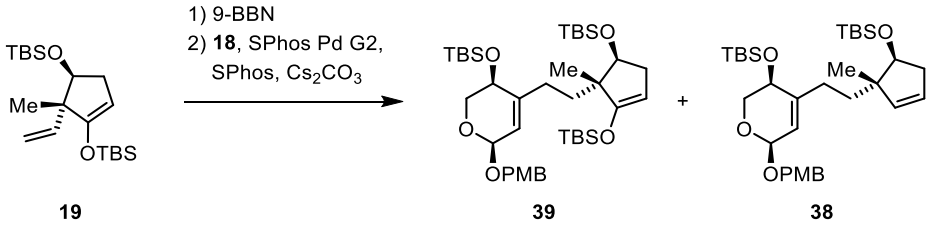
iodide **18** and exposed to the previously established coupling conditions. In an initial attempt, a mixture of the desired coupling product **39** (28% yield) and alkene **38** (69% yield) was obtained (Table 2, entry 1). The alkene functionality of **38** was assumed to be formed by hydroboration of the TBS enol ether (Scheme 8). Presumably, hydroboration of both the exocyclic vinyl group and the TBS enol ether resulted in the formation of intermediate **41**. Elimination of the *β-tert*-butyldimethylsiloxy organoborane then led to the formation of the endocyclic alkene **42**[51] and the following Suzuki−Miyaura cross coupling with vinyl iodide **18** finally afforded the coupling product **38**. By lowering the amount of 9-BBN, this side reaction should be completely suppressed.



Scheme 8. Hydroboration of building block **19** with two equivalents of 9-BBN and subsequent Suzuki−Miyaura cross coupling with vinyl iodide **18**.

To examine the hydroboration step, alkene **19** was treated with different quantities of 9-BBN (Table 2). Monitoring of the hydroboration reaction revealed that 1.3 equivalents of 9-BBN were required for complete consumption of alkene **19**. Since 9-BBN was obtained as a commercially available solution in tetrahydrofuran (THF), we assumed that the concentration of the solution was lower than reported. Treatment of alkene **19** with more than 1.30 equivalents of 9-BBN resulted in the formation of side product **38**. With this optimized hydroboration procedure in hand, coupling product **39** could be obtained in excellent yield (92%) and with high chemoselectivity.

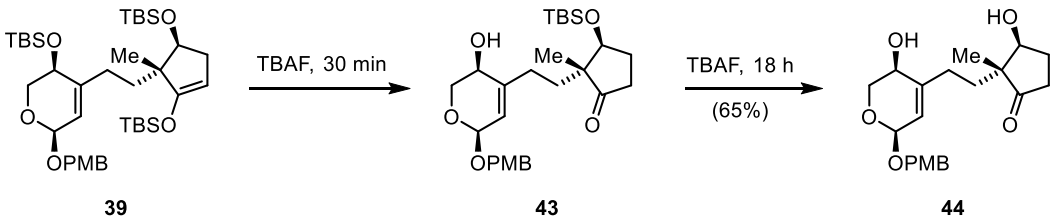
Table 2. Optimization of the *B*-alkyl Suzuki-Miyaura coupling by variations of 9-BBN amounts.



Entry	9-BBN (equiv)	Yield
1[a]	2.00	**39** (28%), **38** (69%)
2[a]	1.05	**39** (44%), **38** (0%)
3[a]	1.30	**39** (81%), **38** (traces)
4[b]	1.30	**39** (92%), **38** (traces)

[a]The reactions were performed on a 0.08 to 0.1 mmol scale using 5 mol% SPhos Pd G2 and 5 mol% SPhos in a mixture of degassed DMF and H_2O (v/v = 9:1). [b]The reaction was performed on a 0.42 mmol scale using 5 mol% SPhos Pd G2 and 5 mol% SPhos in a mixture of degassed DMF and H_2O (v/v = 9:1).

Next, a global deprotection of all three TBS groups of **39** using tetrabutylammonium fluoride (TBAF) was examined (Scheme 9). After 30 min, all starting material was consumed. NMR analysis later revealed that only the allylic silyl ether and the TBS enol ether had been cleaved. We reasoned that steric hindrance of the secondary silyl ether led to prolonged reaction times and thus alcohol **44** could be obtained in good yields by treatment of **39** with excess TBAF over 18 h.

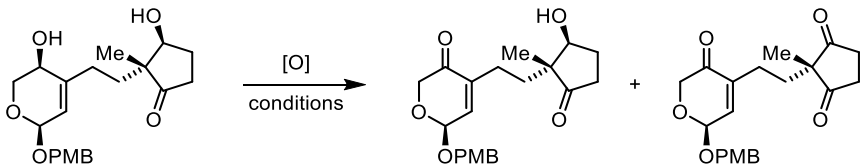


39 **43** **44**

Scheme 9. Deprotection of **39** with TBAF.

The chemoselective oxidation of allylic alcohol **44** was investigated next (Table 3). First, oxidation with DMP resulted in a mixture of products **45** and **46**, with triketone **46** as the major product (entry 1). Fortunately, the oxidation with manganese dioxide (MnO_2) was found to regioselectively afford enone **45** (entry 2).

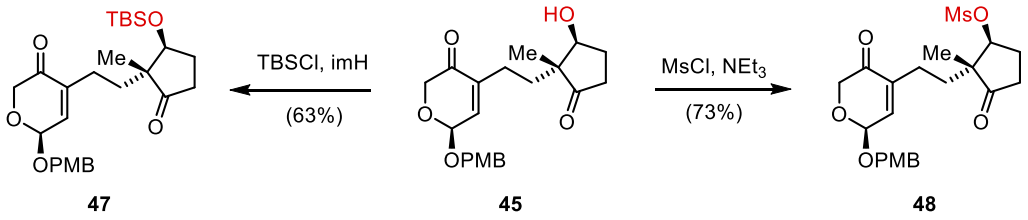
Table 3. Chemoselective oxidation of allylic alcohol **44**.



44 **45** **46**

Entry	Oxidant	Yield
1	DMP (1.2 equiv)	**45** (15%), **46** (56%)
2	MnO_2 (25 equiv)	**45** (54%), **46** (0%)

With enone **45** in hand, TBS protection and mesylation of the alcohol then afforded the two key step precursors **47** and **48** (Scheme 10).

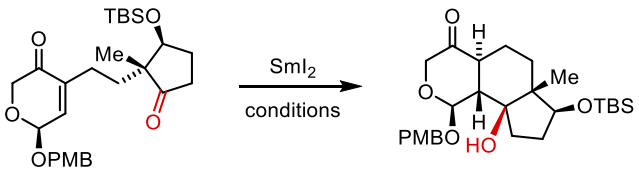


47 **45** **48**

Scheme 10. Preparation of the key step precursors.

Studies for the investigation of the challenging key cyclization-fragmentation cascade were then based on the use of a series of different Sm(II) halides and additives to modulate the reactivity and chemoselectivity of the reductant. In general, the reactivity of Sm(II) reductants has been found to correlate with their thermodynamic redox potentials.[52] $SmCl_2$ (–1.78 eV) and $SmBr_2$ (−1.55 eV) were readily prepared from a solution of SmI_2 (–0.89 eV) in THF by treatment with an excess of anhydrous lithium chloride or bromide, respectively. Initially, enone **47** was subjected to different Sm(II) halides to examine the first step of the cascade reaction (Table 4). Unfortunately, treatment of enone **47** with both SmI_2 and $SmBr_2$ resulted in the formation of complex product mixtures and no cyclization product(s) could be isolated (entries 1, 2). When $SmCl_2$ in *tert*-butanol (*t*-BuOH) was used, no conversion was observed either (entry 3). In a final attempt, enone **47** was subjected to the powerful reductant SmI_2–HMPA (–1.75 eV) in the presence of hexafluoroisopropanol (HFIP), but only a mixture of several unidentified products was isolated (entry 4).

Table 4. Reductive cyclization of ketone **47** with samarium(II) reductants.



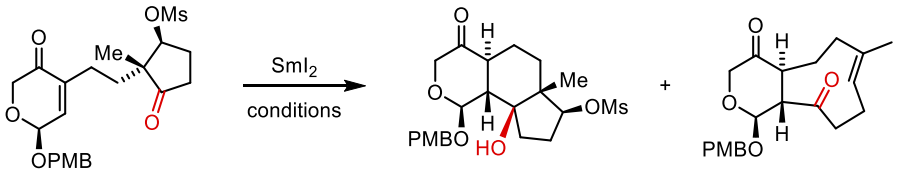
47 **49**

Entry	Additive	T (°C)	t (min)	Observation
1[a]	-	–78	5	complex mixture
2[a]	LiBr (6 equiv/SmI_2)	–78	5	complex mixture
3[b]	LiCl (6 equiv/SmI_2), *t*-BuOH	–78	15	no conversion
4[a]	HMPA (10 equiv), HFIP (2 equiv)	–78	0.5	complex mixture

[a]Addition of SmX_2 to a solution of **47** or addition of **47** to a solution of SmX_2. [b] Addition of **47** to a solution of $SmCl_2$ and *t*-BuOH.

Further attempts to accomplish the cascade reaction with mesylate **48** only afforded a complex mixture of several unidentified products in <5 min at 0 °C or –78 °C, respectively (Table 5). Careful separation by flash column chromatography and HPLC afforded trace amounts of cyclized product **15**.

Table 5. Reductive cyclization of ketone **48** with samarium(II) iodide.



48 **50** **15**

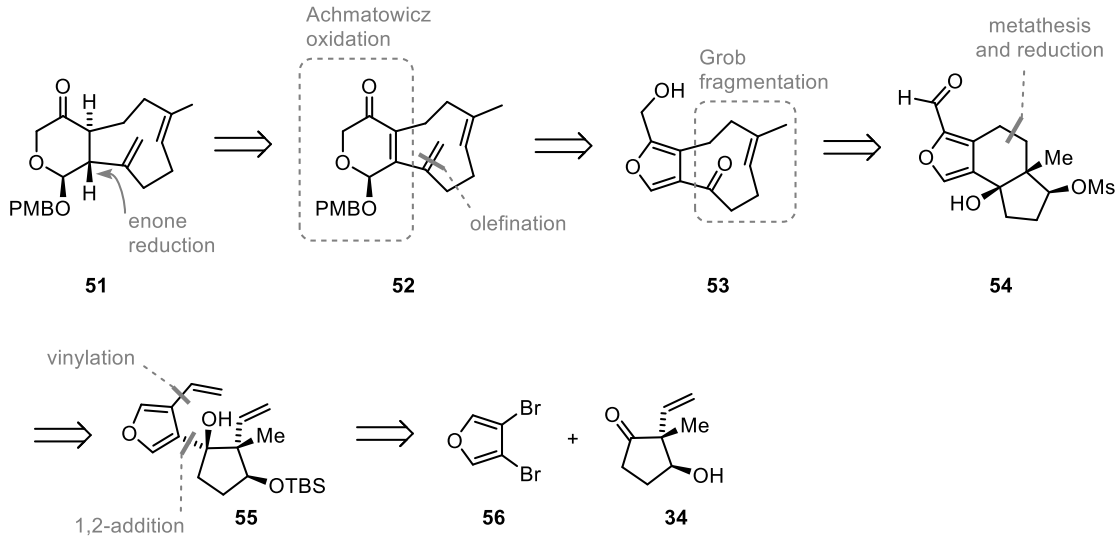
Entry	T (°C)	t (min)	Observation
1	0	5	complex mixture
2[b]	–78	5	complex mixture
3[c]	–78	5	complex mixture
4[d]	–78	60	complex mixture

[b]Addition of SmI_2 to a solution of **48**. [c]Addition of **48** to a solution of SmI_2. [d]Slow addition of **48** over 60 min via syringe pump.

In conclusion, the efficient synthesis of a key intermediate for the synthesis of waixenicin A (**11**) has been accomplished by using a *B*-alkyl Suzuki cross coupling strategy. Nonetheless, the samarium(II) halide-mediated cyclization-fragmentation cascade as key step for the construction of the (*E*)-cyclononene fragment could not be realized. During our cyclization studies, we observed the formation of significant amounts of PMB alcohol and reasoned that the dihydropyran building block could be labile under reductive conditions. Thus, it was envisioned to install the six-membered ring after the fragmentation step.

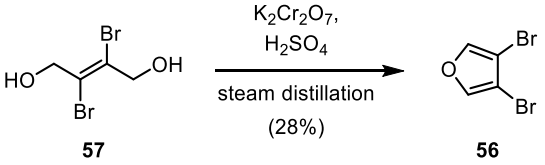
3.2 Second-generation Approach: Furan Oxidation and Grob Fragmentation

For the second-generation strategy, we envisioned to trace waixenicin A (**11**) back to key intermediate **53**, which contains the (*E*)-cyclononene ring fused to a furan ring (Scheme 11). In this strategy, installation of the dihydropyran ring should be realized by a late-stage Achmatowicz oxidation of the furfuryl alcohol to give dihydropyranone **52**. Reduction of the enone should afford the 6,9-bicyclic core structure **51** of the natural product. The construction of the (*E*)-cyclononene ring should again be achieved by a stereospecific Grob fragmentation of precursor **54**. Further dissection of this tricycle by an intramolecular olefin cross metathesis and a 1,2-addition of a 3-lithiated 3,4-dihalofuran would lead back to two building blocks: 3,4-dibromofuran (**56**) and already prepared functionalized cyclopentanone **34**.



Scheme 11. Second-generation retrosynthetic analysis of a common intermediate of waixenicin A (**11**).

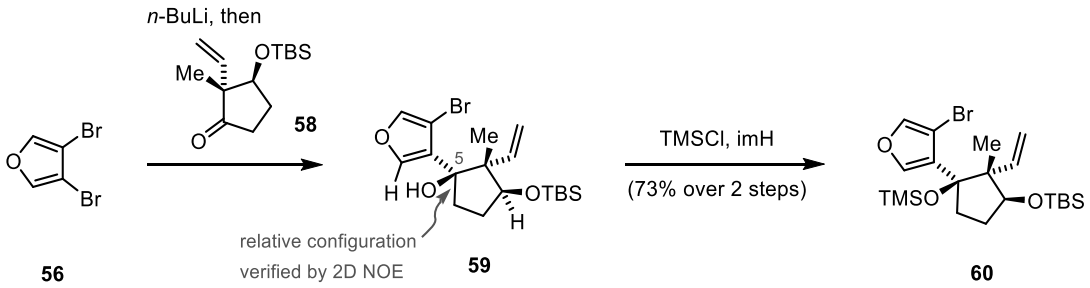
Our synthetic route commenced with the preparation of 3,4-dibromofuran (**56**) from commercially available *trans*-2,3-dibromo-2-butene-1,4-diol (**57**) by oxidation and aromatization with chromic acid (Scheme 12).[53] The product was extracted from the reaction mixture by steam distillation. Although the reaction afforded 3,4-dibromofuran (**56**) in low yield (28%), this transformation was found to be a reliable way to prepare >10 g of the furan building block in one day.



Scheme 12. Synthesis of 3,4-dibromofuran (**56**).

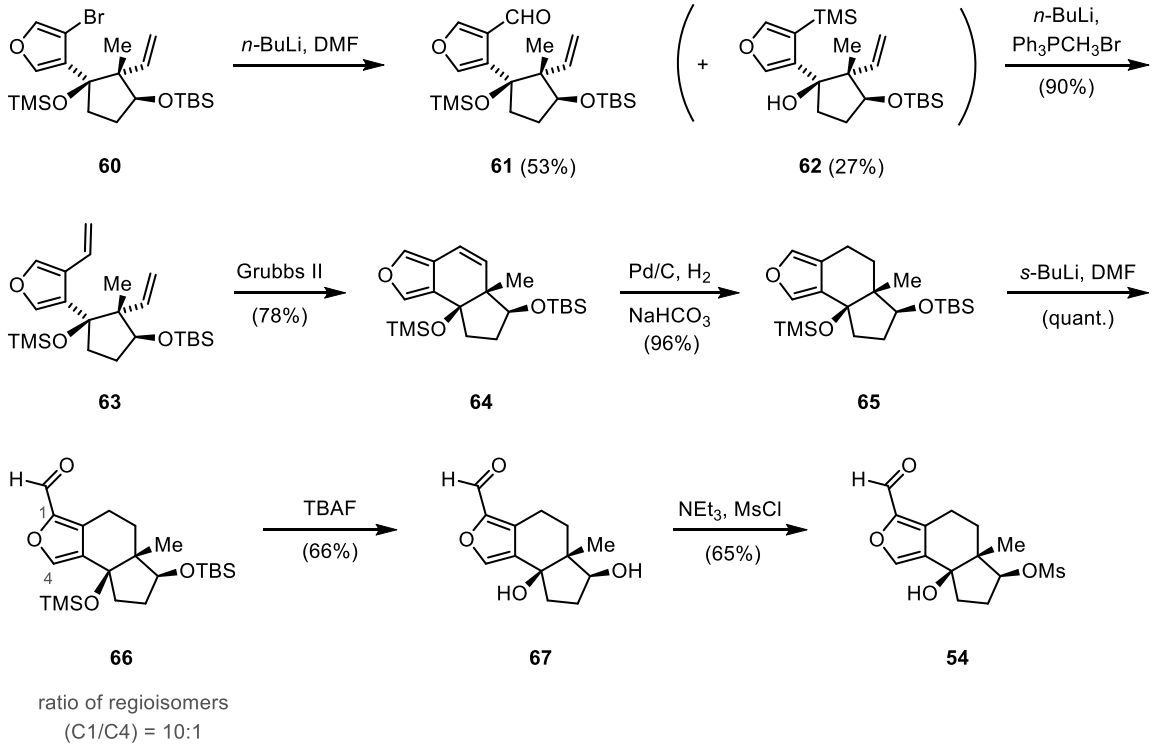
On a 2 g scale, 3,4-dibromofuran (**56**) was coupled to ketone **58** via bromine-lithium exchange and subsequent attack of the generated lithium species on the ketone. The resultant alcohol **59** was

obtained as a single diastereomer and converted to its trimethylsilyl (TMS) ether **60** under standard silylation conditions (TMSCl, imH) (Scheme 13). The relative configuration of the newly installed stereogenic center at C5 position was verified by NOESY experiments.



Scheme 13. Synthesis of 3-bromofuran **60**.

The following formylation with dimethylformamide (DMF) proceeded in moderate yield (53%) to furnish aldehyde **61** (Scheme 14). A competing retro-Brook rearrangement lowered the yield of this transformation and resulted in the formation of side product **62**. All attempts to suppress this side reaction by performing the reaction in less polar solvents (e.g. hexanes/diethyl ether = 1:1) had no effect.



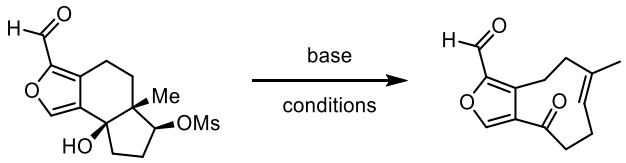
Scheme 14. Synthesis of tricycle **54**.

Next, a high-yielding Wittig olefination and an ensuing olefin metathesis using Grubbs second generation catalyst under optimized reaction conditions afforded 5,6,5-tricycle **64** in high yield. Hydrogenation of the double bond and regioselective formylation of the furan ring using *sec*-butyl

lithium and DMF afforded aldehyde **66**. The global deprotection of the silyl ethers was best achieved using TBAF and gave diol **67**. Regioselective conversion of the tertiary alcohol to mesylate **54** proceeded in good yield under optimized reaction conditions.

With fragmentation precursor **54** in hand, the envisioned key step for the construction of the nine-membered carbocyclic ring was investigated (Table 6). However, treatment of aldehyde **54** with different bases (NaH, KO*t*-Bu or KHMDS) either resulted in no conversion (entries 1, 2) or in decomposition (entries 3, 4).

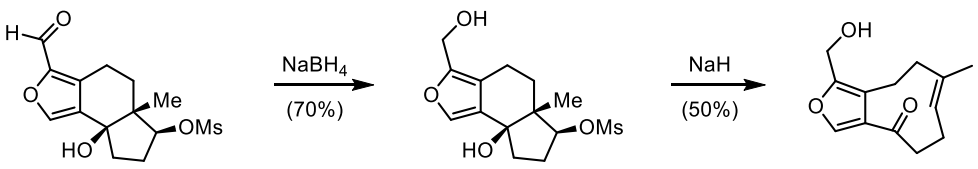
Table 6. Fragmentation of alcohol **54**.



54 **68**

Entry	Base (equiv)	Solvent	Observation
1	KHMDS (1.1)	THF	no reaction
2	NaH (1.1)	DMF	no reaction
3	NaH (2.0)	DMF	decomposition
4	KO*t*-Bu (1.0)	*t*-BuOH	decomposition

Aldehyde **54** was therefore reduced to primary alcohol **69** with sodium borohydride in good yield. In a first attempt, fragmentation product **53** could be obtained in 50% yield by using two equivalents of sodium hydride (Scheme 15). All attempts to further optimize this transformation by employing different bases (e.g. KO*t*-Bu in *t*-BuOH, KHMDS in THF) did not provide better yields.



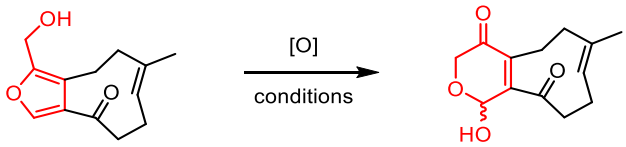
54 **69** **53**

Scheme 15. Successful construction of the (*E*)-cyclononene ring.

With bicycle **53** in hand, the ensuing key Achmatowicz rearrangement[54,55] could be investigated (Table 7). Unfortunately, oxidative ring expansion of the furfuryl alcohol in the presence of either

N-bromosuccinimide (NBS)[56] or VO(acac)$_2$/*tert*-butylhydroperoxide (TBHP)[57] resulted in decomposition (entries 1, 2). In order to perform the reaction chemoselectively at the furan moiety, a singlet oxygen-induced Achmatowicz rearrangement protocol[58,59] was employed. However, a complex product mixture was obtained when the photooxygenation of furfuryl alcohol **53** was performed at –78 °C (entry 3). 2D NMR analysis revealed the formation of different products resulting from an ene reaction of the trisubstituted C–C double bond with singlet oxygen.

Table 7. Conditions for the oxidative rearrangement of furan **53**.

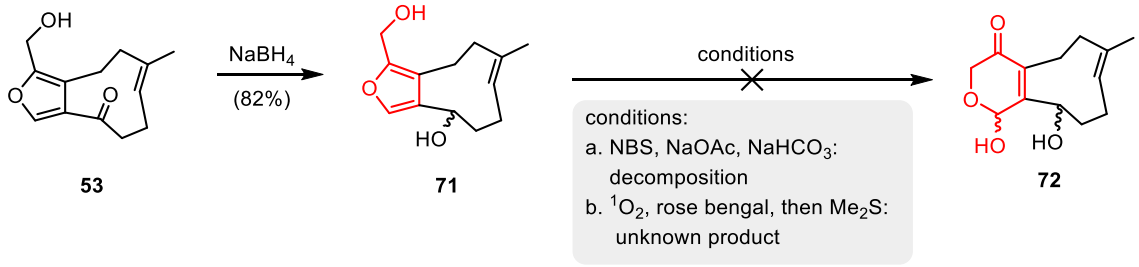


53 **70**

Entry	Conditions	T (°C)	Observation
1	NBS, NaOAc, $NaHCO_3$	23	decomposition
2	$VO(acac)_2$, TBHP	0 to 23	decomposition
3	$^1O_2$,[a] then Me_2S	–78 to 0	unidentified products

[a]Singlet oxygen ($^1O_2$) was generated using rose bengal as photosensitizer and by irradiation with a Replux Belgium RL 160 W lamp.

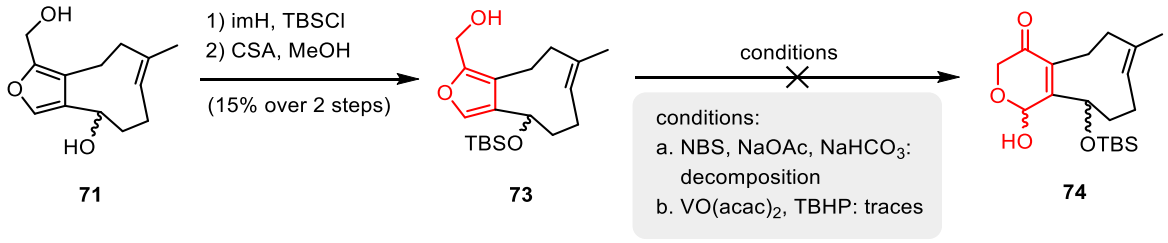
To determine the influence of the benzylic ketone on the oxidative ring expansion, ketone **53** was reduced to the corresponding alcohol **71** by treatment with sodium borohydride. However, no product formation was observed when the Achmatowicz rearrangement was performed with NBS or VO(acac)$_2$/TBHP (Scheme 16).



53 **71** **72**

Scheme 16. Reduction of the benzylic ketone to alcohol **71** and subsequent Achmatowicz rearrangement.

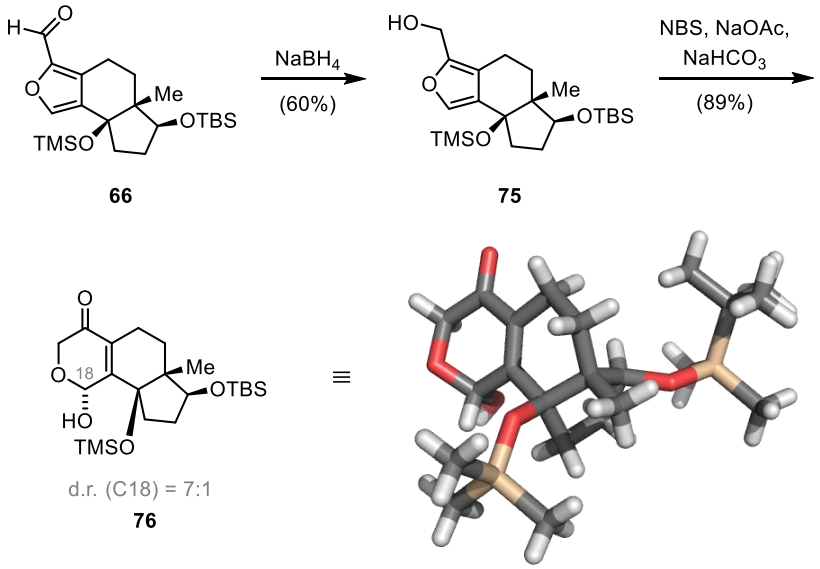
We next employed a two-step procedure to afford TBS ether **73**. Unfortunately, no product formation was observed when furfuryl alcohol **73** was subjected to different oxidative ring expansion conditions (Scheme 17).



71 73 74

Scheme 17. Synthesis of TBS ether **73** and attempted oxidative ring expansion of the furan moiety.

Cirumventing difficulties with the oxidation of the furan ring in the presence of the cyclononene, the Grob fragmentation should be performed after conversion of the furan to the dihydropyran. Thus, aldehyde **66** was reduced to primary alcohol **75** by treatment with sodium borohydride (Scheme 18). The following oxidative rearrangement of furfuryl alcohol **75** to dihydropyranone **76** was successfully realized using stoichiometric quantities of recrystallized NBS, supplemented by addition of sodium acetate and sodium bicarbonate to buffer the hydrobromic acid formed.[56] Using these conditions, the corresponding dihydropyranone **76** could be obtained in excellent yield (89%) and with good diastereoselectivity (d.r. = 7:1, major diastereomer is shown in Scheme 18). Single crystal X-ray analysis of the major diastereomer of dihydropyranone **76** also confirmed the configuration of the hydroxyl group of the lactol moiety.



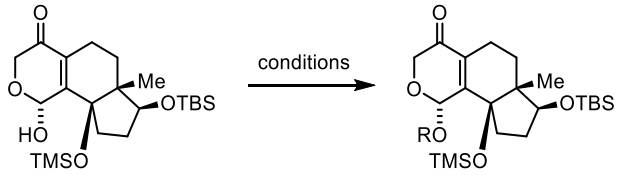
66 75 76

Scheme 18. Synthesis and molecular structure of dihydropyranon **76**.

Protection of the lactol functionality was next investigated (Table 8). First, a methyl and PMB group were chosen as protecting groups due to their stability toward a variety of conditions. However, methylation using methyl iodide or PMB protection using Dudley's reagent II[60] were low-yielding (Table 8, entries 1, 2). We next converted lactol **76** to acetal **77c** by treatment with acetic anhydride under basic conditions in very good yield (entry 3). A palladium-catalyzed

transacetalization with PMB alcohol[39] should then install the PMB group, but this reaction proved to the difficult and no conversion was observed (entry 4). We then decided to install a benzoate protecting group (entry 5). The introduction of silyl ethers was also investigated, but TBS protection of the lactol was unsuccessful (entries 6, 7). However, TMS-protection of lactol **76** could be performed with high yield (entry 8).

Table 8. Introduction of a variety of protecting groups on the lactol moiety of **76**.



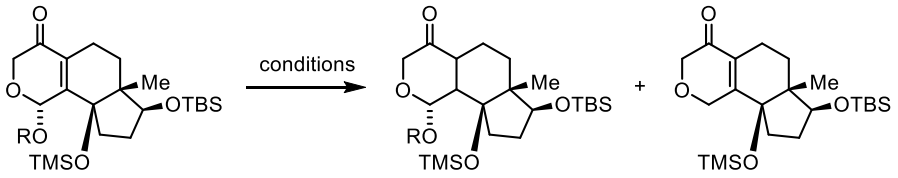
76 **77a–f**

Entry	R	Electrophile	Reagent(s)	Product	Yield
1	Me	MeI	Ag_2O	**77a**	25%
2	PMB	Dudley II	MgO, MeOTf	**77b**	15%
3	Ac	Ac_2O	py, DMAP	**77c**	85%
4	PMB	PMBOH	$Pd(OAc)_2$, $P(OPh)_3$	**77b**	0%
5	Bz	BzCl	py, DMAP	**77d**	97%
6	TBS	TBSCl	$AgNO_3$, py	**77e**	0%
7	TBS	TBSOTf	2,6-lutidine	**77e**	0%
8	TMS	TMSCl	$AgNO_3$, py	**77f**	95%

With a range of substrates in hand, we investigated the hydrogenation of the tetrasubstituted double bond in enones **76**, **77a**, **77d** and **77f** (Table 9). First, hydrogenation reactions under heterogeneous conditions using 10% palladium on charcoal (Pd/C) or platinum oxide (PtO_2) as catalysts were investigated. For the hydrogenation reactions with Pd/C, an excess of sodium bicarbonate (up to four equivalents) was added to prevent hydrolysis of the acetal. Hydrogenation of enone **77a** at 1 bar in either ethyl acetate or methanol resulted in no conversion (entries 1, 2). The rate of hydrogenation reactions is generally increased at elevated hydrogen pressure. However, no reduction of the double bond of tricycle **77a** was observed at 8 bar, 18 bar or 80 bar, respectively (entries 3−5). The use of PtO_2 as catalyst in a mixture of methanol and THF at 10 bar hydrogen pressure also resulted in no conversion (entry 6). Decomposition of the substrate was observed when lactol **76** was used (entry 7). Hydrogenation of benzoate **77d** resulted in no reaction at 1 bar hydrogen pressure, but hydrogenation in an autoclave under higher pressure (5 bar) surprisingly

led to a mixture of products, containing dihydropyran **79** as the major product (entries 8, 9). We next investigated homogeneous hydrogenation with Crabtree's catalyst[61] ([Ir(PCy$_3$)(py)(cod)]PF$_6$) and the BAr$_F$-variant thereof, using either benzoate **77d**, TMS acetal **77f** or lactol **76**. However, no hydrogenation of the different enones was observed (entries 10–13). The use of (*S*,*S*)-[Rh(Et-DuPhos)(cod)]BF$_4$ as catalyst was also unsuccessful (entry 14).

Table 9. Hydrogenation of different enones.

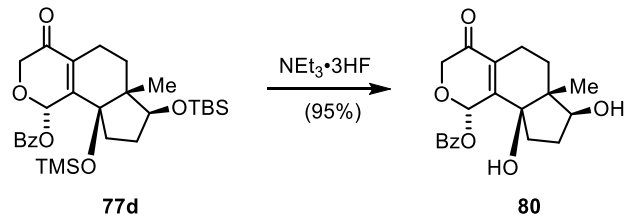


76, **77a–f** **78** **79**

Entry	R	Catalyst	Additive	H_2 Pressure	Solvent	Observation
1	Me	Pd/C	$NaHCO_3$	1 bar	EtOAc	no conversion
2	Me	Pd/C	$NaHCO_3$	1 bar	MeOH	no conversion
3	Me	Pd/C	$NaHCO_3$	8 bar	THF	no conversion
4	Me	Pd/C	$NaHCO_3$	18 bar	THF	no conversion
5	Me	Pd/C	$NaHCO_3$	80 bar	THF	no conversion, slow decomp.
6	Me	PtO_2	-	10 bar	MeOH, THF	no conversion
7	H	Pd/C	$NaHCO_3$	1 bar	MeOH	decomposition
8	Bz	Pd/C	$NaHCO_3$	1 bar	THF	no conversion
9	Bz	Pd/C	$NaHCO_3$	5 bar	THF	**79** (traces)
10	Bz	[Ir(PCy$_3$)(py)(cod)]PF$_6$	-	1 bar	CH_2Cl_2	no conversion
11	H	[Ir(PCy$_3$)(py)(cod)]PF$_6$	-	1 bar	CH_2Cl_2	no conversion
12	H	[Ir(PCy$_3$)(py)(cod)]PF$_6$	-	15 bar	CH_2Cl_2	no conversion
13	TMS	[Ir(PCy$_3$)(py)(cod)]BAr$_F$	-	60 bar	$Cl(CH_2)_2Cl$	deprotection of tert. TMS ether
14	TMS	(*S*,*S*)-[Rh(Et-DuPhos)(cod)]BF$_4$	-	60 bar	$Cl(CH_2)_2Cl$	deprotection of TMS acetal
15	TMS	Pd/C	$NaHCO_3$	1 bar	EtOAc	no conversion
16	TMS	Pd/C	$NaHCO_3$	35 bar	EtOAc	no conversion

Additionally, we examined the hydrogenation of TMS lactol **77f** under hetereogenous conditions. To our surprise, **77f** was found to be stable under buffered hydrogenation conditions. However, even hydrogenation at 35 bar (22 h in ethyl acetate) was unsuccessful and only starting material was recovered (entries 15, 16).

By looking at the molecular structure of lactol **76** (Scheme 18), we concluded that hydrogenation of the double bond might occur from the more accessible *β*-face, which is also sterically shielded by the TMS ether of the acetal moiety. Thus, a global deprotection of the silyl ethers should provide a substrate with less steric encumbrance. Furthermore, the free tertiary hydroxyl group could direct hydrogenation from the *α*-face. The synthesis of diol **80** was realized by treatment of benzoate **77d** with triethylamine trihydrofluoride (Scheme 19).

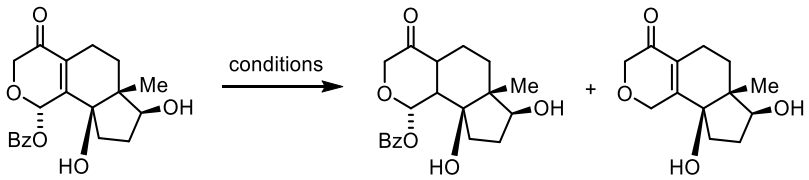


77d **80**

Scheme 19. Global deprotection of the silyl ethers.

However, hydrogenation of diol **80** using Pd/C only resulted in partial elimination of benzoic acid (Table 10, entry 1). When Crabtree's catalyst was used, either no conversion (entry 2) or decomposition of the substrate was observed (entry 3).

Table 10. Hydrogenation of diol **80**.

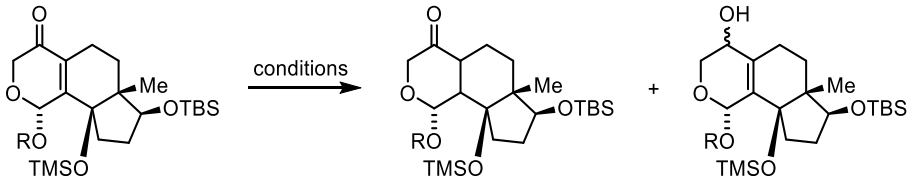


80 **81** **82**

Entry	Catalyst	H_2 Pressure	Solvent	Observation
1	Pd/C	1 bar	THF	**82** (traces)
2	Crabtree	1 bar	CH_2Cl_2	no conversion
3	Crabtree	6 bar	CH_2Cl_2	decomposition

Given the difficulties encountered with heterogeneous and homogeneous hydrogenation reactions, we next examined various 1,4-reduction protocols (Table 11). First, transition metal-mediated reductions with sodium borohydride were investigated. Treatment of enone **77d** with copper(II) chloride and sodium borohydride resulted in a mixture of several products, with allylic alcohol **83** as the major product (entry 1). The use of cobalt(II) chloride and sodium borohydride resulted in no conversion when the reaction was performed in water and in decomposition with methanol as solvent (entries 2, 3). Additionally, the use of *in situ* generated copper(I) hydride from copper(II) acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf) and tetramethyldisiloxane (TMDS) proved to be ineffective (entry 4). Although few examples for the reduction of tetrasubstituted enones with copper(I) hydrides are known, we reasoned that sterical hindrance of the enone might prohibit their reaction. Next, Shenvi's mild protocol for the radical hydrogenation of alkenes using manganese(III) or cobalt(II) catalysts was employed.[62] However, no conversion was observed for benzoate **77d** and lactol **76**, even when a large excess of the reagents was used (entries 5, 6).

Table 11. Conditions for the 1,4-reduction of enones **76** and **77a,d**.



76, 77a,d **78** **83**

Entry	R	Metal salt	Reducing agent	Solvent	Observation
1	Me	$CuCl_2$	$NaBH_4$	EtOH	1,2-reduction
2	Bz	$CoCl_2 \cdot 6H_2O$	$NaBH_4$	H_2O	no conversion
3	Bz	$CoCl_2 \cdot 6H_2O$	$NaBH_4$	MeOH	decomposition
4	Bz	$Cu(OAc)_2$, dppf	TMDS	THF	no conversion
5	Bz	$Mn(dpm)_3$	$PhSiH_3$	*i*-PrOH	no conversion
6	H	$Mn(dpm)_3$	$PhSiH_3$	*i*-PrOH	no conversion

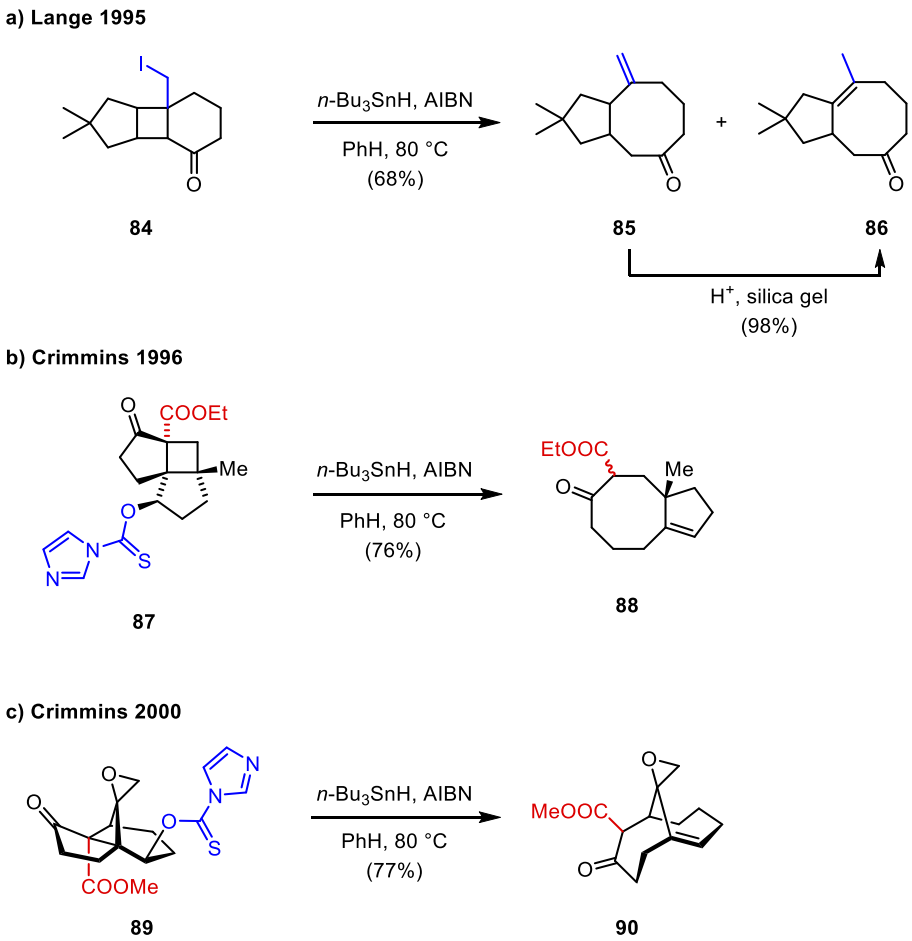
In conclusion, a Grob fragmentation of a tricyclic monomesylated 1,3-diol afforded the desired (*E*)-configured cyclononene present in waixenicin A (**11**), which was fused to a furan ring. Nonetheless, a regioselective oxidation of the furan moiety for the construction of the dihydropyran could not be achieved. On the other hand, oxidation of the furan ring of the tricyclic fragmentation precursor afforded the corresponding tricyclic enone. However, the steric hindrance of the

tetrasubstituted double bond and the lability of the dihydropyran unit toward both acids and bases made reduction of the enone very challenging.

3.3 Third-generation Approach: Radical and Grob Fragmentations

3.3.1 Radical Fragmentations

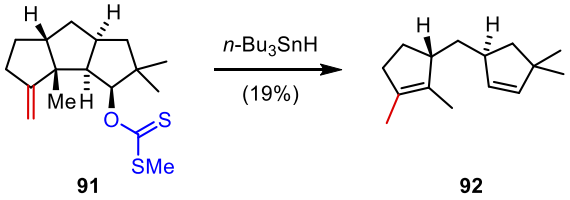
While the use of radical cyclizations for the synthesis of medium-sized rings has been extensively studied over the past few decades, radical fragmentations have not found widespread application.[63] Some selected examples are shown in Scheme 20. For example, Lange and Crimmins both reported the fragmentation of tricyclic compounds containing a cyclobutane unit under free radical conditions to construct eight-membered carbocycles in the 1990s (Scheme 20a, b).[64–66] As radical precursors, they employed either thiocarbamates, xanthates or alkyl iodides. The utilization of this strategy was further demonstrated by Crimmins in 2000, where a ten-membered ring was prepared by radical fragmentation of xanthate **89** (Scheme 20c).[67]



Scheme 20. Exemplary radical fragmentation reactions.

In general, radicals can easily break C−C bonds when they are generated adjacent to a strained ring, such as a cyclobutane ring. However, the C−C bond of larger rings can also be cleaved if the resulting radical is appropriately stabilized, as exemplified by Reddy et al. (Scheme 21).[68] Thereby,

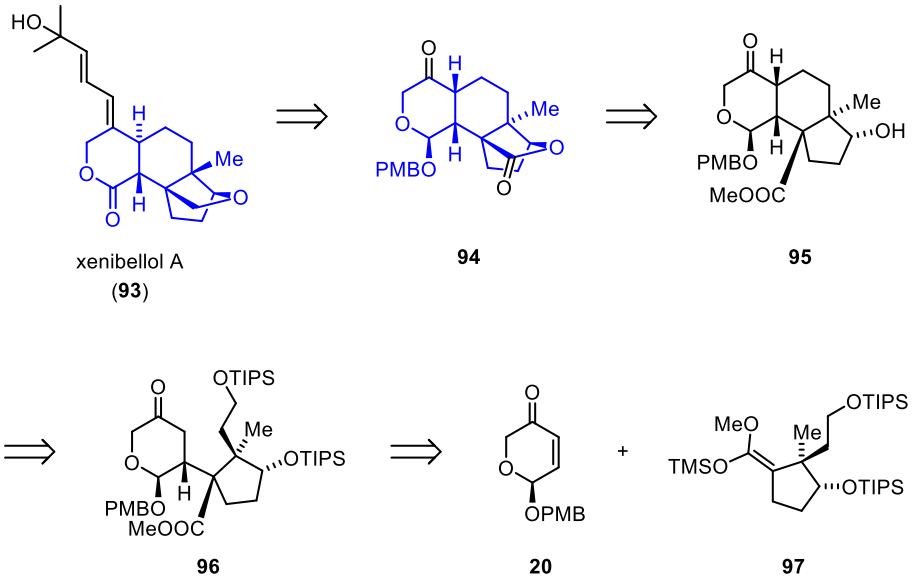
the fragmentation only occurs when the single occupied molecular orbital (SOMO) of the radical efficiently overlaps with the σ-orbital of the C−C bond that should be cleaved.[69]



91 **92**

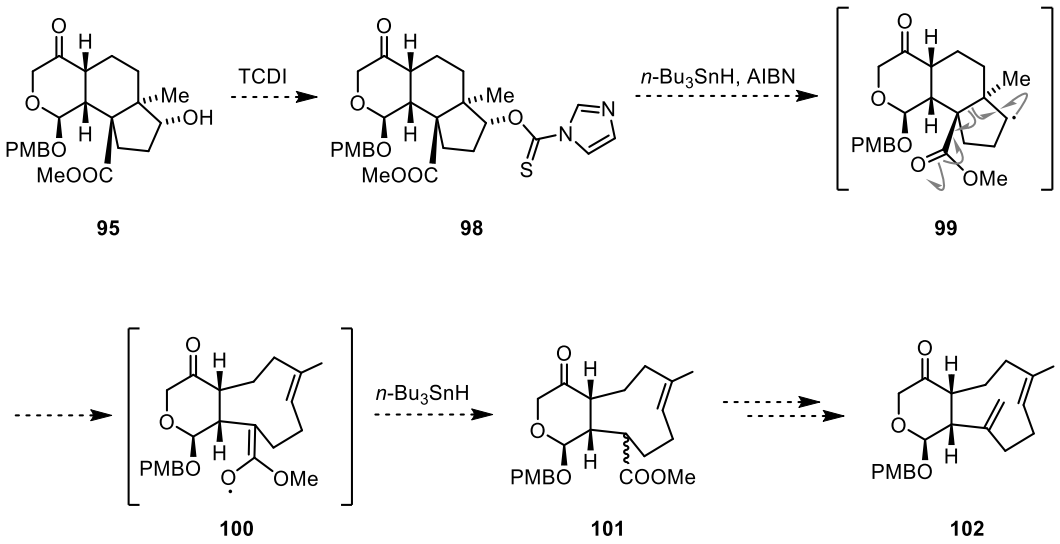
Scheme 21. Radical fragmentation of 5,5,5-tricyle **91**.

During extensive studies directed toward the total synthesis of the xeniolide xenibellol A (**93**) together with Simon Schnell, a master student in the group of Prof. Thomas Magauer, the *epi*-methyl core structure (**94**) of this natural product (highlighted in blue color) could be successfully prepared from two building blocks: known enone **20** and TMS ketene acetal **97** (Scheme 22).[70]



Scheme 22. Studies toward the synthesis of xenibellol A (**93**).

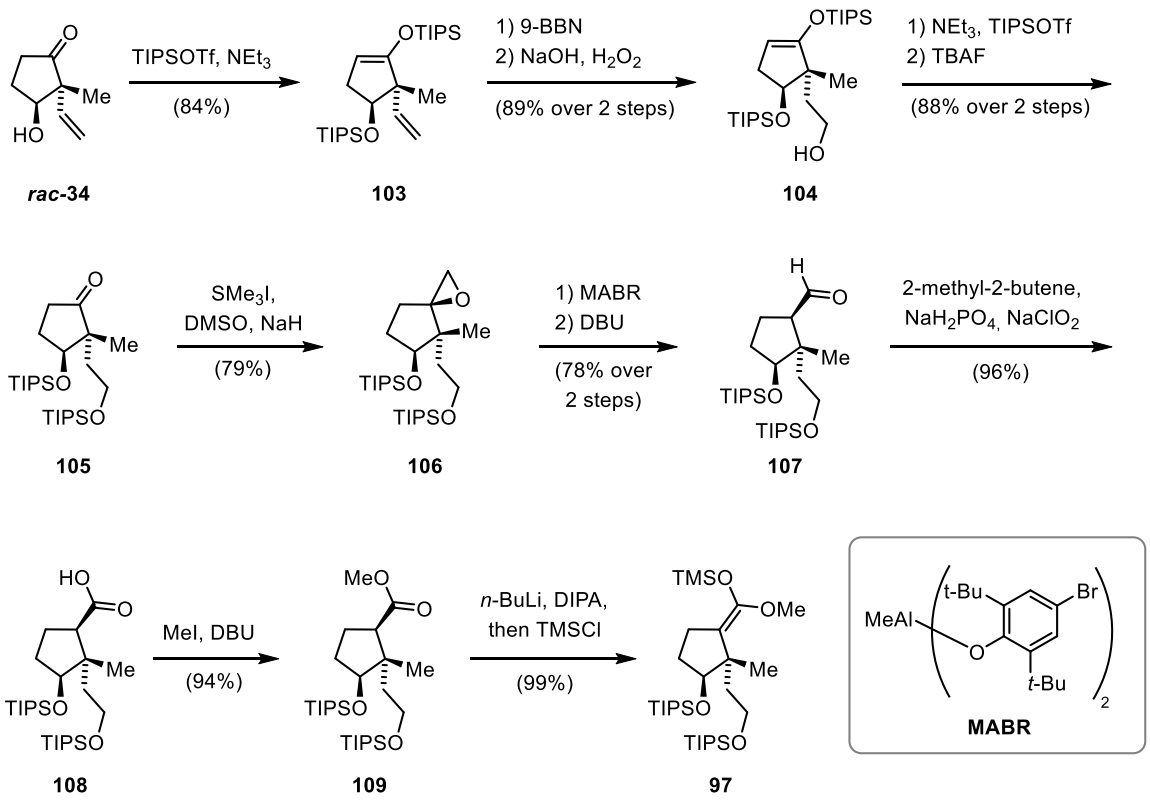
We now envisioned using tricyclic alcohol **95**, an intermediate in the synthesis of tetracycle **94**, as a versatile precursor for radical fragmentation reactions to construct the nine-membered carbocycle of waixenicin A (**11**). In our approach, an ester functionality should be used as radical stabilizing substituent. For this synthetic strategy, we envisioned to convert alcohol **95** to thiocarbamate **98**, which should then fragment under free radical conditions to afford the 6,9-bicyclic core structure **101** of waixenicin A (Scheme 23).



Scheme 23. Planned radical fragmentation for the construction of the bicyclic core structure of waixenicin A (**11**).

For the synthesis of radical fragmentation precursor **98**, two building blocks had to be prepared. First, the preparation of TMS ketene acetal **97** is illustrated in Scheme 24. Previously prepared hydroxyketone ***rac*-34**[**] was TIPS-protected and the exocyclic vinyl group was further functionalized by a hydroboration/oxidation sequence (***rac*-34→104**). Protection of the generated primary alcohol **104** as TIPS ether, followed by chemoselective deprotection of the TIPS enol ether afforded ketone **105** in good yield. The required C_1-elongation of the ketone was then achieved by conversion to epoxide **106**, which was further transformed to aldehyde **107** by a Lewis acid-mediated stereocontrolled epoxide rearrangement. The use of several different Lewis acids for this transformation was examined,[††] but the best results were achieved with the exceptionally bulky Lewis acid MABR (= methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)).[71] The reaction afforded aldehyde **107** as a mixture of diastereomers (d.r. = 1:1.4), which could be epimerized with DBU to the major diastereomer shown in Scheme 24. The aldehyde was then oxidized to the corresponding carboxylic acid **108**, followed by conversion to methyl ester **109**. The formation of TMS ketene acetal **97** was best achieved by treatment of methyl ester **109** with a freshly prepared solution of LDA as base in a highly concentrated solution and by subsequent trapping of the generated ester enolate with freshly distilled TMSCl.

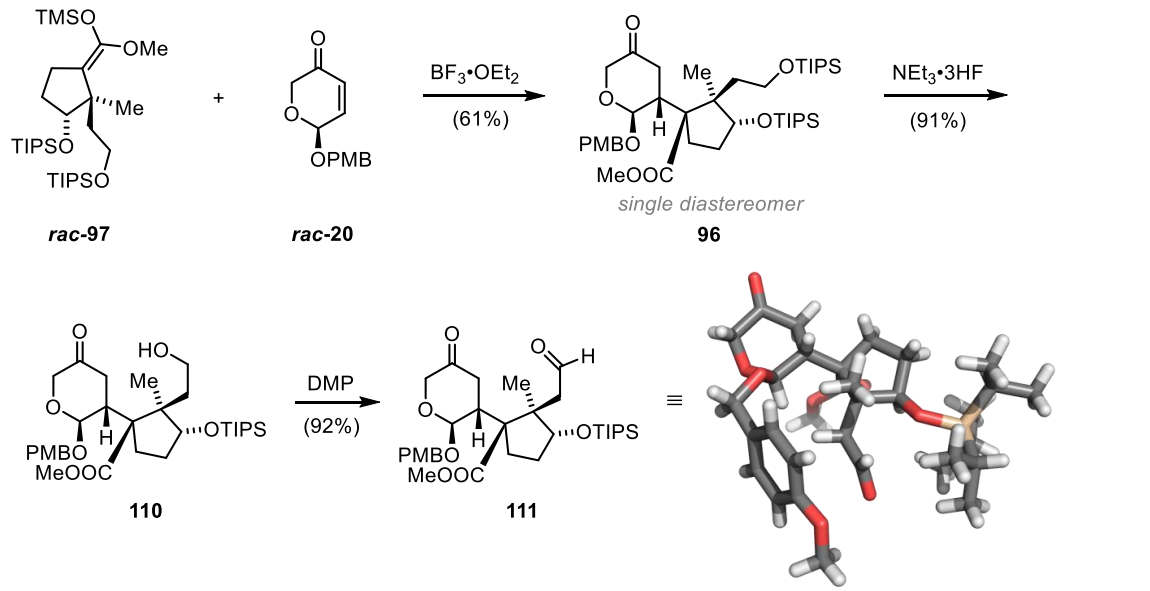
[**] Cyclopentanone **34** was prepared in racemic fashion for the studies presented in this chapter. All other compounds are also racemic and only one enantiomer is shown.
[††] The screening of different Lewis acids for this transformation was carried out by Fabian Hernichel.



Scheme 24. Synthesis of TMS ketene acetal **97**.

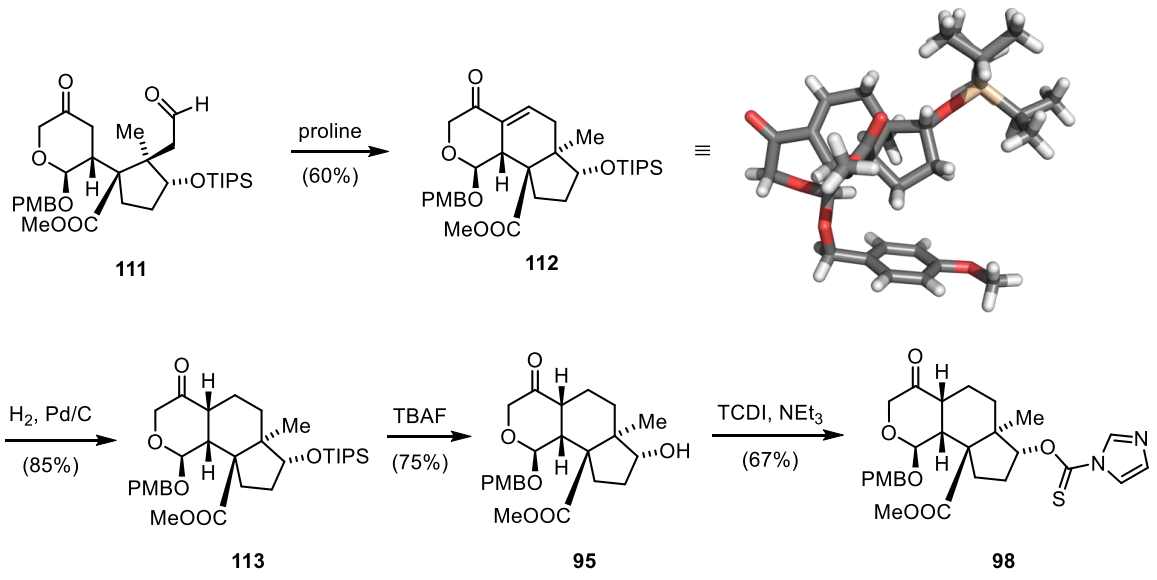
An extensive screening for the realization of the following key step, a Mukaiyama−Michael reaction between previously prepared racemic enone ***rac*-20** and racemic TMS ketene acetal **97**, resulted in the diastereoselective preparation of ketone **96** by using stoichiometric amounts of boron trifluoride etherate. Chemoselective deprotection of the primary TIPS ether, followed by oxidation gave aldehyde **111**.[‡‡] The structure of aldehyde **111** was further verified by single crystal X-ray analysis (Scheme 25).

[‡‡] Optimization of the synthetic steps shown in Scheme 25 and 26 was carried out by Simon Schnell.



Scheme 25. Synthesis of aldehyde **111** and its molecular structure.

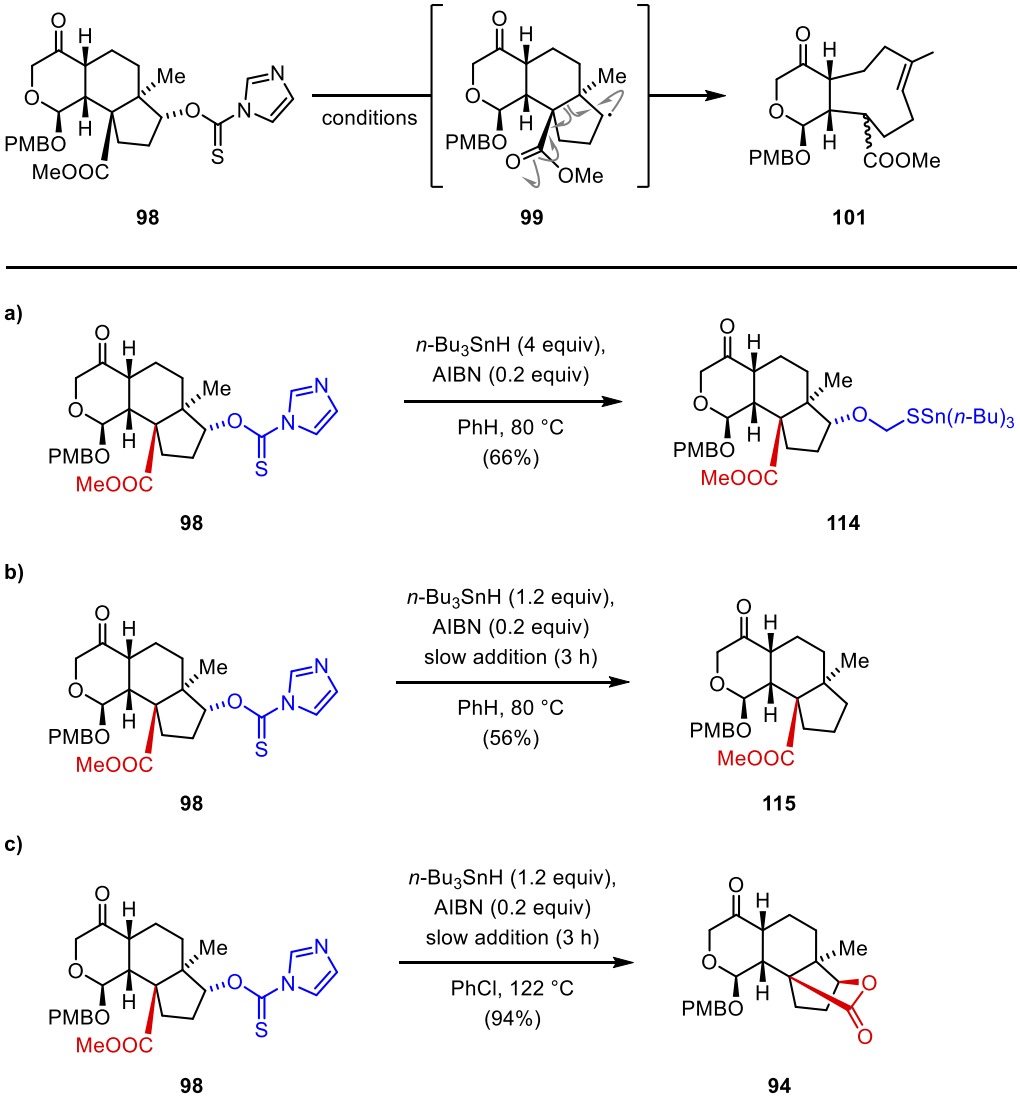
With aldehyde **111** in hand, a proline-catalyzed aldol condensation resulted in the construction of tricycle **112**, as proven by X-ray diffraction of a single crystal of **112** (Scheme 26). The enone moiety was then reduced to ketone **113** by palladium-catalyzed hydrogenation. Deprotection of the secondary alcohol and conversion to thiocarbamate **98** afforded the first precursor for the envisioned radical fragmentation.



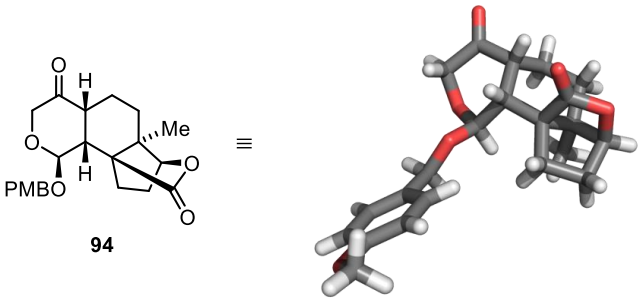
Scheme 26. Synthesis of thiocarbamate **98**.

With thiocarbamate **98** in hand, fragmentation to bicycle **101** under radical conditions was first examined by premixing the substrate with excess tributyltin hydride (*n*-Bu_3SnH)/AIBN and by heating to 80 °C. However, mixed *O*,*S*-acetal **114** was isolated as the only product (Scheme 27a).

Trying to avoid this side reaction, a mixture of *n*-Bu_3SnH and AIBN in benzene was added dropwise via syringe pump to a refluxing solution of thiocarbamate **98** in benzene. The reaction cleanly afforded a single product, which was assigned to be tricycle **115** (Scheme 27b). Although the secondary radical was generated, no fragmentation occurred. By performing the reaction in chlorobenzene at 122 °C, the fragmentation should be more facile and might precede hydrogen abstraction. Instead, γ-lactone **116** was obtained in 94% yield and its structure was verified by single crystal X-ray analysis (Schemes 27c and 28). This reaction presumably proceeded via an S_N2-type attack of the ester carbonyl at the thiocarbamate and displayed another competing side reaction for the fragmentation.

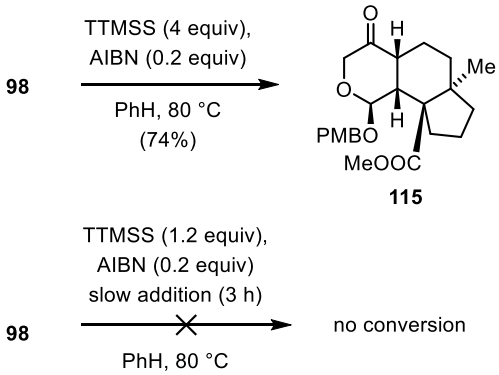


Scheme 27. Screening of radical fragmentation reactions.



Scheme 28. Molecular structure of tetracycle **94**.

Next, the reaction was performed with TTMSS (= tris(trimethylsilyl)silane)[62] instead of tributyltin hydride as hydrogen donor. The dissociation energy of the Si−H bond in TTMSS is slightly higher (79 kcal/mol)[72] than the dissociation energy of the Sn−H bond strength in *n*-Bu_3SnH (74 kcal/mol) and therefore, TTMSS is a slower hydrogen donor than *n*-Bu_3SnH. Unfortunately, only the product resulting from hydrogen abstraction (**98→115**) was isolated in good yields when the reaction was performed in refluxing benzene (Scheme 29).



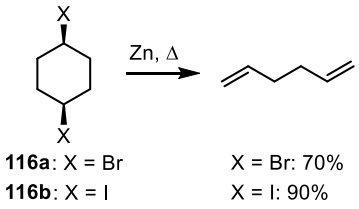
Scheme 29. Attempted radical fragmentation reactions with TTMSS (= tris(trimethylsilyl)silane).

In conclusion, the utilization of a radical fragmentation for the synthesis of the nine-membered ring of waixenicin A (**11**) was found to be very challenging. This could be a consequence of the low thermodynamic driving force for the radical fragmentation of cyclopentanes as compared to cyclobutanes.

3.3.2 Grob Fragmentation

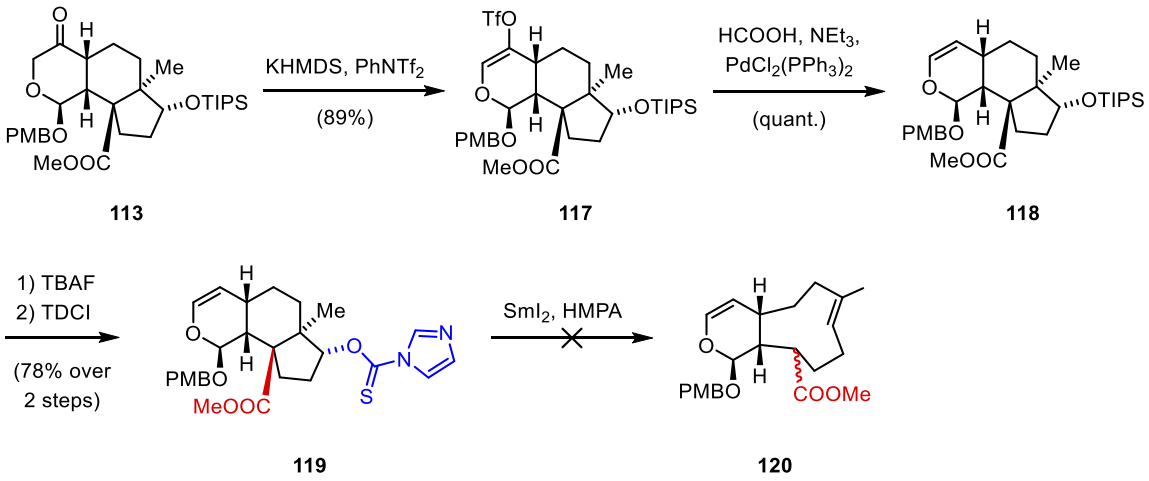
In previous chapters, the Grob fragmentation of monomesylated 1,3-diols has been studied. This strategy has been successfully employed for the synthesis of the (*E*)-cyclononene fragment of waixenicin A (see chapter 3.2). In addition to the use of 1,3-diols as fragmentation precursors, other 1,3-diheterosubstituted substrates can also undergo Grob fragmentations.[42] For example, in 1955, Grob and Baumann demonstrated that *cis*-1,4-dibromocyclohexane (**116a**) and *cis*-1,4-

diiodocyclohexane (**116b**) could be fragmented to hexa-1,5-diene upon treatment with zinc (Scheme 30).[73]



Scheme 30. Grob fragmentation of *cis*-1,4-dihalocyclohexanes **116a** and **116b** with zinc.

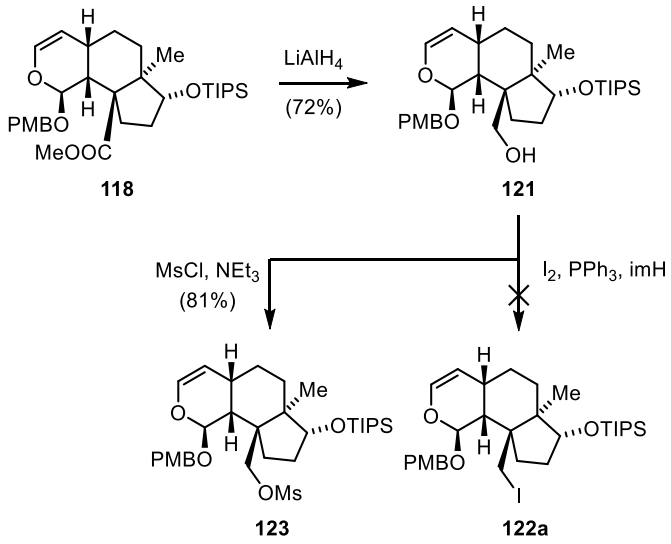
Based on this discovery, we decided to investigate a similar fragmentation by generating the carbanion in a different way. We envisioned to investigate the use of samarium diiodide (SmI_2) as reductant for the utilization of a Grob fragmentation. The SmI_2-HMPA complex has been described to efficiently reduce xanthates to carbanions via two SETs.[74] For the preparation of a suitable substrate for the SmI_2-mediated fragmentation, the ketone had to be converted to the corresponding enol ether. Otherwise a reaction of the ketone with SmI_2 would lead to the formation of a ketyl radical which would interfere with the fragmentation reaction. Thus, tricycle **113** was converted to vinyl triflate **117** which was smoothly reduced to enol ether **118** (Scheme 31). Deprotection of the TIPS ether and introduction of the thiocarbamate then delivered fragmentation precursor **119**.



Scheme 31. Samarium(II) iodide-mediated Grob-type fragmentation.

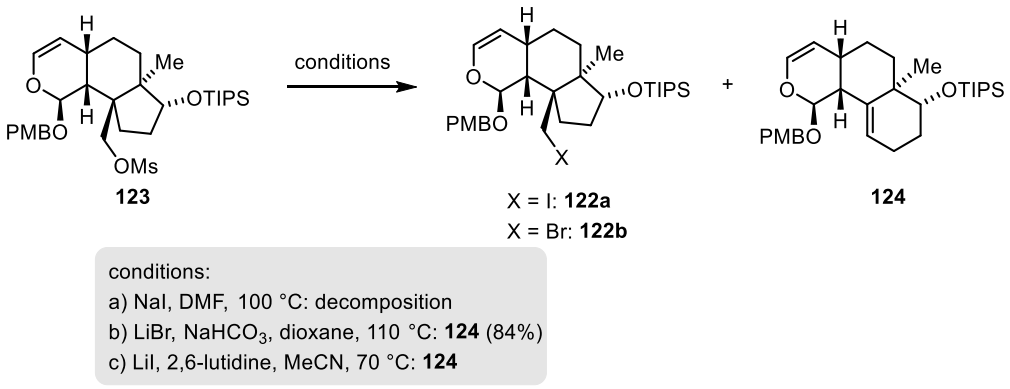
However, dropwise addition of the substrate to a premixed solution of excess SmI_2 and HMPA only resulted in hydrolysis of the thiocarbamate. The use of freshly dried HMPA produced the same result. Given the difficulties encountered with the Grob fragmentation of xanthates, we next investigated the conversion of the ester group to the corresponding primary halide. Zinc insertion or reduction with SmI_2 should then generate a primary carbanion, which should readily fragment to give an exo-methylene group and thus generate the nine-membered carbocycle.

First, reduction of ester **118** with an excess of lithium aluminum hydride afforded primary alcohol **121**, which should be further converted to iodide **122**. However, only decomposition of the substrate was observed under Appel's conditions. The enol ether moiety of the six-membered ring was presumably not tolerated under these conditions. We therefore prepared mesylate **123** by treatment of alcohol **121** with mesyl chloride and triethylamine (Scheme 32).



Scheme 32. Formation of primary alcohol **121**, attempted iodination and successful mesylation.

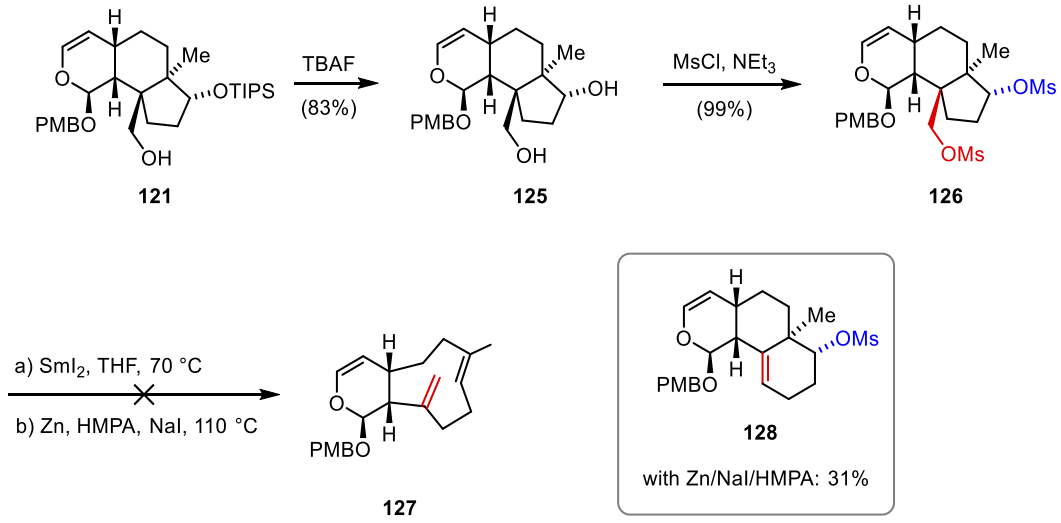
Next, conversion of the mesylate to the corresponding bromide or iodide was examined. While the reaction of mesylate **123** with sodium iodide in DMF resulted in decomposition, the use of additives (e.g. $NaHCO_3$ or 2,6-lutidine) to trap *in situ* generated hydroiodic acid resulted in the formation of rearranged alkene **124**, a side product that is sometimes observed for neopentylic sulfonates or halides (Scheme 33).



Scheme 33. Formation of alkene **124** under Finkelstein conditions.

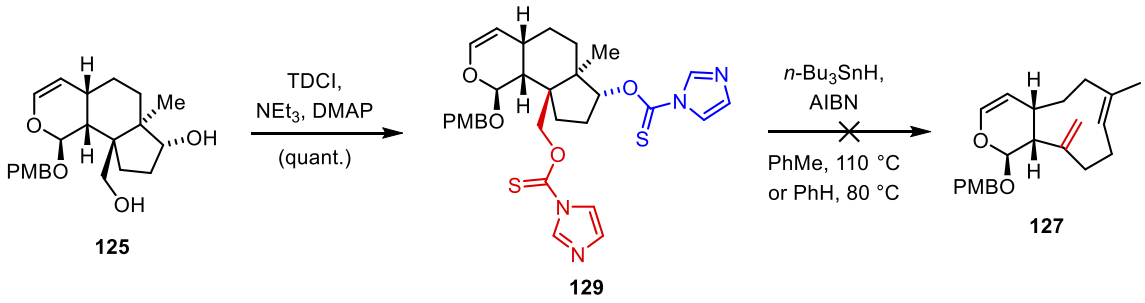
As an alternative to the use of halides for the generation of carbanions by metal insertion or reduction, mesylates can be reduced to carbanions by using a mixture of activated zinc, HMPA and

sodium iodide in refluxing DMF.[75] We therefore prepared dimesylate **126** from diol **125** by deprotection of the TIPS ether, followed by mesylation of the two hydroxyl groups (Scheme 34). When dimesylate **126** was subjected to these rather harsh conditions, at least two new products were formed with alkene **128** as the major product. Unfortunately, it was not possible to avoid the formation of the undesired rearrangement product. Furthermore, when dimesylate **126** was added to a refluxing solution of SmI_2 in THF, only slow and sluggish conversion of **126** was observed and this strategy was not further pursued. Treatment of dimesylate **126** with Zn/HMPA/NaI at 110 °C resulted in the isolation of low amounts of rearrangement product **128**.



Scheme 34. Attempted fragmentation of dimesylate **126**.

In a final attempt, diol **125** was converted to bisthiocarbamate **129** and was subjected to radical fragmentation reactions by using *n*-Bu_3SnH/AIBN at 80 °C or 110 °C, but only decomposition was observed (Scheme 35).



Scheme 35. Attempted radical fragmentation of bisthiocarbamate **129**.

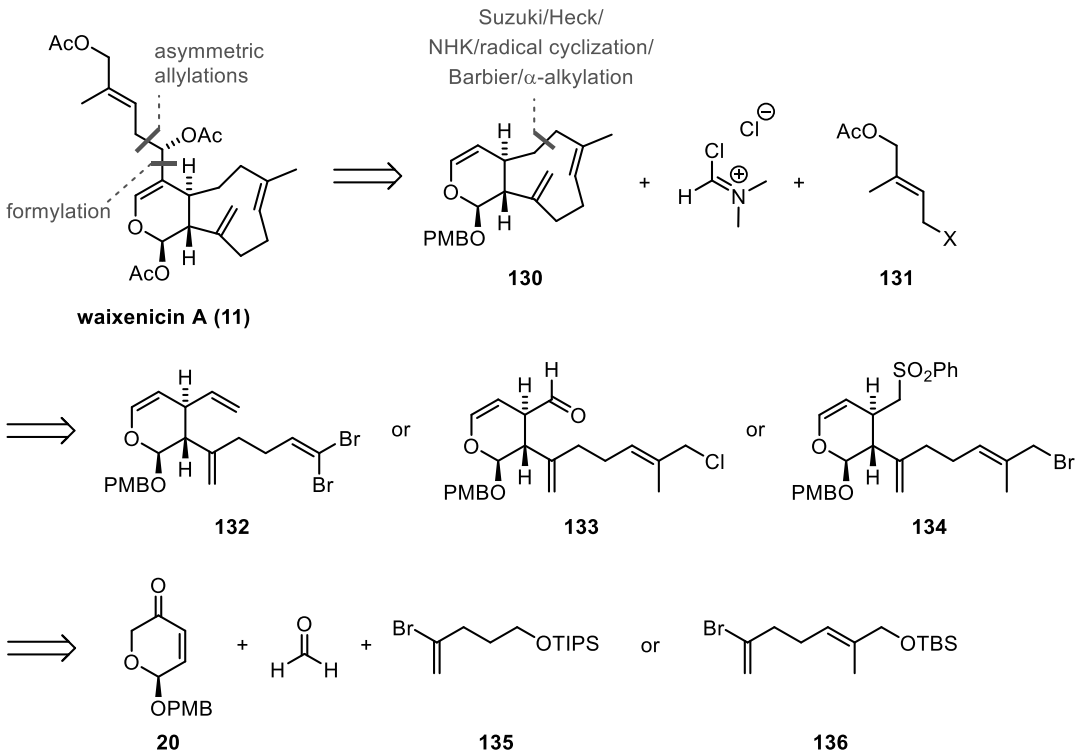
In conclusion, several tricyclic precursors for the investigation of a radical or Grob fragmentation to construct the (*E*)-cyclononene fragment of waixenicin A (**11**) have been prepared. Extensive fragmentation studies under free radical conditions revealed that although the generation of the

secondary alkyl radical was successful, no fragmentation occurred. All further attempts to realize a Grob fragmentation using SmI_2 or zinc as reductants were also found to be challenging.

3.4 Fourth-generation Approach: Cyclization of Acyclic Precursors

In previous synthetic studies directed toward the construction of the 6,9-bicyclic scaffold of waixenicin A (**11**), the application of a Grob fragmentation for the assembly of the (*E*)-cyclononene fragment was found to be challenging (see chapters 3.1, 3.2, 3.3). In this approach, the direct synthesis of (*E*)-cyclononenes from acyclic precursors will be examined. Circumventing steric constraints and entropic barriers[37] remains the major challenge in the direct ring closure of nine-membered rings and general methods have not been described so far. Previous studies aimed at the synthesis of xeniolides and structurally related natural products made use of an intramolecular Tsuji–Trost allylation,[76] an intramolecular *B*-alkyl Suzuki coupling[77] and a Nozaki–Hiyama–Kishi coupling[78] for the construction of the nine-membered carbocycle from acyclic precursors.

Our plans for the synthesis of waixenicin A (**11**) were designed to investigate the utilization of different ring closing reactions for the direct construction of (*E*)-cyclononenes from acyclic substrates by *B*-alkyl Suzuki coupling,[79] Heck reaction,[80] Barbier reaction,[81] Nozaki−Hiyama−Kishi (NHK) reaction, radical cyclization reactions and α-alkylation reactions in parallel. The (*E*)-configured trisubstituted alkene should be installed in the acyclic precursor by olefination and should remain intact during the ring closing reactions. A general retrosynthetic analysis is shown in Scheme 36.

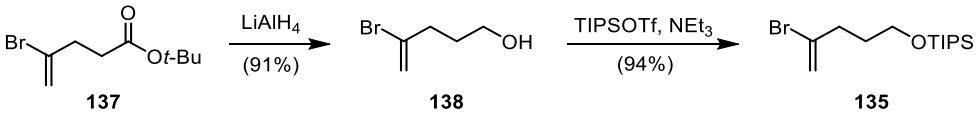


Scheme 36. Retrosynthetic analysis of waixenicin A (**11**).

The side chain of waixenicin A (**11**) should be introduced by formylation of enol ether **130**, followed by asymmetric allylation. The bicyclic core structure of the natural product should be accessed by different ring closing reactions as described above. The different cyclization precursors could be traced back to the three general building blocks: literature-known enone **20**, formaldehyde as C_1-building block and vinyl bromides **135** or **136**, respectively. Functionalization of enone **20** by conjugate addition of vinyl bromide **135** or **136** and subsequent trapping of the generated enolate with formaldehyde should give access to the three precursors **132**, **133** and **134** for the key steps.

3.4.1 *B*-Alkyl Suzuki Cross Coupling

Following our retrosynthetic plan, the employment of the *B*-alkyl Suzuki cross coupling and the intramolecular Heck reaction for the formation of the nine-membered ring was investigated. Thus, a two-step procedure for the synthesis of vinyl bromide **135** was established (Scheme 37). Reduction of literature-known ester **137** using $LiAlH_4$,[82] followed by TIPS-protection of generated alcohol **138** afforded building block **135**.

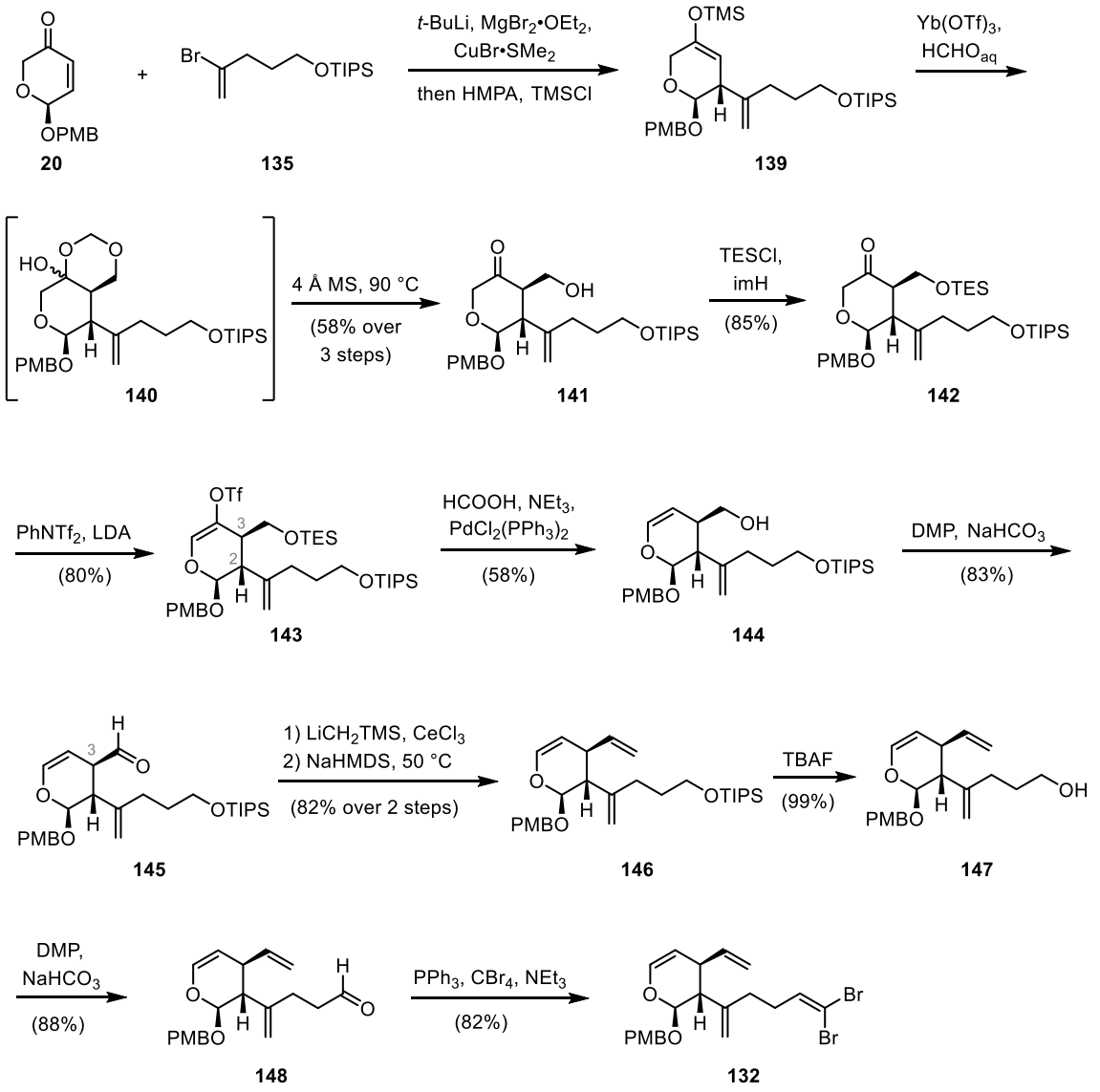


137 138 135

Scheme 37. Two-step procedure to access vinylbromide **135**.

Conjugate addition of vinyl bromide **135** to enantiopure enone **20** and subsequent trapping of the generated enolate with TMSCl afforded TMS enol ether **139** (Scheme 38). Treatment with an aqueous formaldehyde solution in the presence of catalytic amounts of ytterbium(III) triflate then resulted in the formation of a product mixture containing *β*-hydroxy ketone **141** and products resulting from formaldehyde over-addition, such as lactol **140**. However, excess formaldehyde could be removed by heating the reaction to 90 °C in the presence of 4 Å molecular sieves to give *β*-hydroxy ketone **141** in good yield over three steps and in gram quantities.[83] TES-protection of the alcohol and triflation of the ketone using LDA and $PhNTf_2$ afforded triflate **143**. Remarkably, the two contiguous stereocenters at the C2 and C3 position of the natural product could be installed via this diastereoselective sequence. The synthesis of the dihydropyran fragment was then finalized by reduction of the triflate to the corresponding enol ether **144**. For the synthesis of the Suzuki−Miyaura and Heck coupling precursors, the primary alcohol of **144** was oxidized to aldehyde **145**, which was further transformed to an exocyclic vinyl group. The olefination of aldehyde **145** proved to be challenging and initial Wittig or Horner reactions led to inseparable mixtures of unidentified products. The use of $LiCH_2TMS$ afforded a mixture of recovered aldehyde **145** and its conjugated isomer. Finally, a cerium(III)-modified Peterson olefination

procedure[84] could be successfully employed. Premixing cerium(III) chloride and $LiCH_2TMS$, followed by addition of aldehyde **145** afforded a diastereomeric *β*-hydroxy silane, which generated alkene **146** upon treatment with NaHMDS. No epimerization at the C3 position was observed. Deprotection of the TBS ether with TBAF and oxidation of the generated alcohol afforded aldehyde **148**, which was converted to dibromoalkene **132**. The addition of triethylamine was found to be crucial for the success of this transformation.

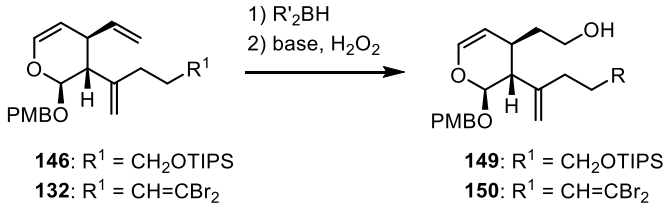


Scheme 38. Synthesis of dibromolefin **132**.

With substrate **132** in hand, the reactivity of the vinyl group was explored by applying different hydroboration conditions (Table 12). To our surprise, the vinyl group proved to be sterically more hindered than expected. Hydroboration under standard conditions (9-BBN, 25 °C) resulted in no conversion (entry 1). Prolonged reaction times or heating to 60 °C resulted in slow conversion to multiple products (entries 2, 3). To exclude the undesired reactivity from the dibromoalkene, we

also investigated the use of substrate **146**. Again, 9-BBN displayed poor reactivity toward the sterically congested alkene **146** at 25 °C or 60 °C, respectively (entries 4, 5). When dicyclohexylborane (Cy_2BH) was used, formation of a new product was observed (entry 6). 2D NMR studies indicated that hydroboration occurred not only at the vinyl group, but also at the enol ether moiety. The use of milder reaction conditions by treating alkene **132** with catecholborane in the presence of Wilkinson's catalyst[85] resulted in no conversion (entry 7). In conclusion, chemoselective hydroboration of the vinyl group was not possible under standard conditions and we therefore turned our attention to a different approach.

Table 12. Hydroboration studies.



146: $R^1 = CH_2OTIPS$
132: $R^1 = CH{=}CBr_2$

149: $R^1 = CH_2OTIPS$
150: $R^1 = CH{=}CBr_2$

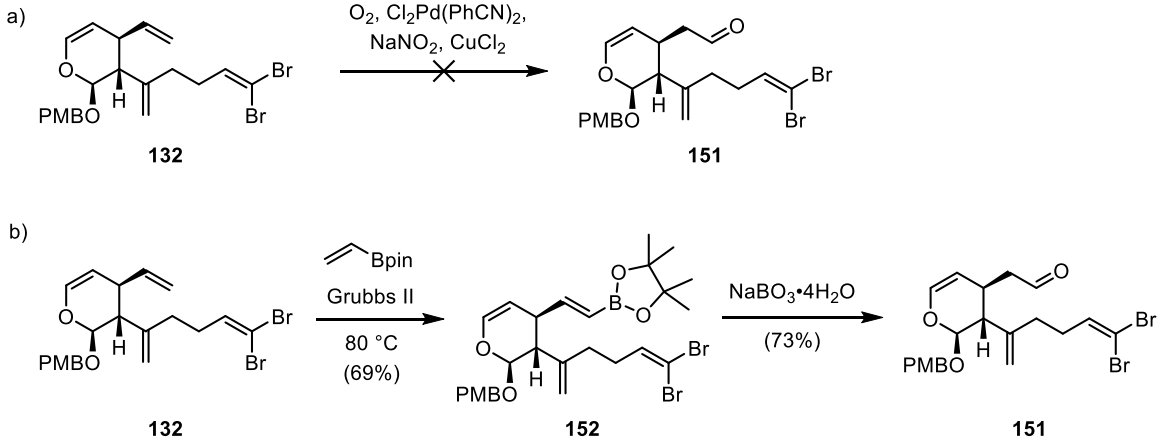
Entry	Substrate	Reagents[a]	T (°C)	t (h)	Observation
1	**132**	9-BBN	25	3	no reaction
2	**132**	9-BBN	25	24	decomposition
3	**132**	9-BBN	60	5	decomposition
4	**146**	9-BBN	25	24	no reaction[b]
5	**146**	9-BBN	60	3	no reaction
6	**146**	Cy_2BH	25	24	40% unidentified product
7	**132**	catecholborane, $(Ph_3P)_3RhCl$	25	24	no reaction

[a]All reactions were performed in THF. Oxidation of the borane species with 3 M aqueous sodium hydroxide solution (9 equiv) and hydrogen peroxide (30 wt% in water, 9 equiv) at 25 °C for 1 to 2 h. [b]61% starting material was recovered by flash column chromatography.

3.4.2 Nozaki–Hiyama–Kishi (NHK) Coupling

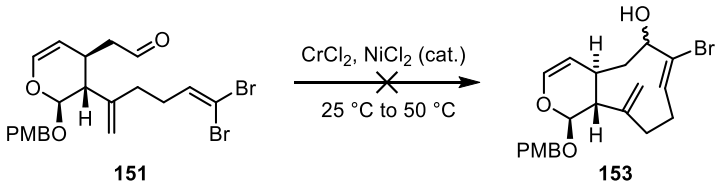
Another approach was examined by the conversion of alkene **132** to aldehyde **151** as precursor for an intramolecular NHK reaction. First, alkene **132** was subjected to aldehyde-selective Wacker oxidation conditions (Scheme 39a),[86] but no conversion was observed. A two-step procedure consisting of a regioselective olefin cross metathesis reaction of alkene **132** with vinylboronic acid

pinacol ester, followed by oxidative hydrolysis of the resulting boronic ester successfully furnished aldehyde **151** (Scheme 39b). With this substrate in hand, we next investigated the intramolecular NHK coupling.



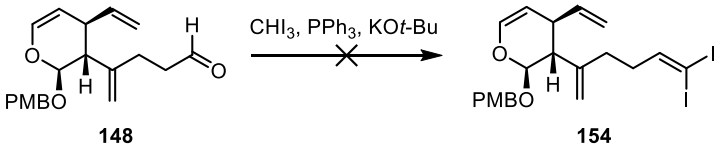
Scheme 39. Oxidation of terminal alkene **132** to aldehyde **151**.

Treatment of aldehyde **151** with chromium(II) chloride and catalytic amounts of nickel(II) chloride should induce the ring closure and form the nine-membered ring. However, no conversion was observed (Scheme 40).



Scheme 40. Attempted NHK coupling of **151**.

The preparation of the corresponding diiodoalkene to facilitate the oxidative addition of Ni(0) into the carbon-halide bond was also unsuccessful (Scheme 41).

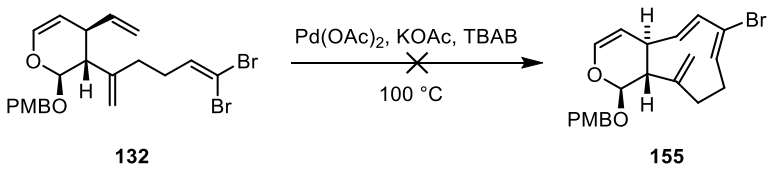


Scheme 41. Attempted preparation of diiodoalkene **154**.

In parallel, we also investigated the application of a Heck reaction.

3.4.3 Intramolecular Heck Reaction

In general, the 8-*exo-trig* cyclization is favored over the 9-*endo-trig* cyclization in intramolecular Heck reactions. This can be mainly attributed to a lesser steric hindrance associated with the intermediate palladacycle in the 8-*exo-trig* cyclization mode.[87] Nevertheless, the use of phosphine-free[88–90] palladium(0)-catalyzed Heck coupling conditions was found to result in the formation of nine-membered rings via the 9-*endo-trig* cyclization mode.[91] This reaction, however, is highly substrate-dependent and no generally applicable method for the synthesis of nine-membered carbocycles via intramolecular Heck reaction has been described to date. Unfortunately, alkene **132** decomposed under the harsh reaction conditions and no cyclization was observed (Scheme 42).

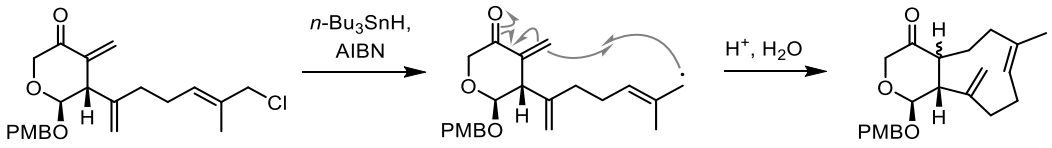


132 **155**

Scheme 42. Attempted 9-*endo* Heck cyclization.

3.4.4 Radical Cyclization

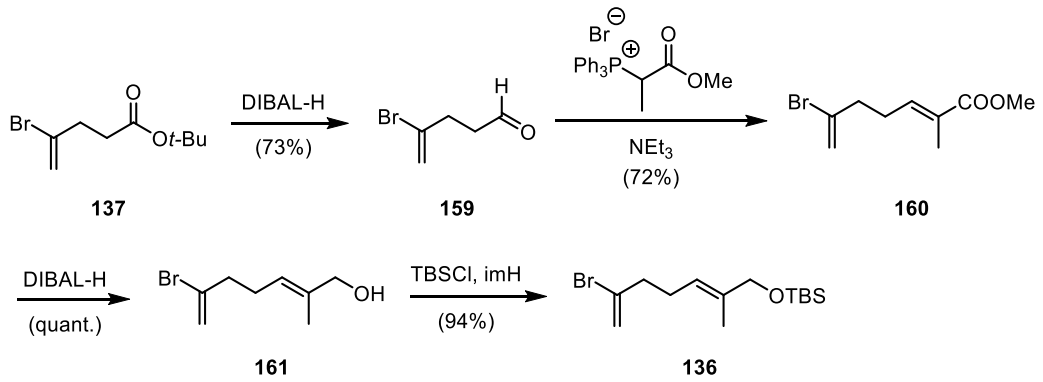
In another approach, we envisioned closing the nine-membered ring by means of a radical cyclization of chloro enone **156**. Generation of an allylic radical from an allylic chloride using free radical conditions and subsequent cyclization onto the *exo*-enone moiety, should afford the desired cyclononene motif (Scheme 43).



156 **157** **158**

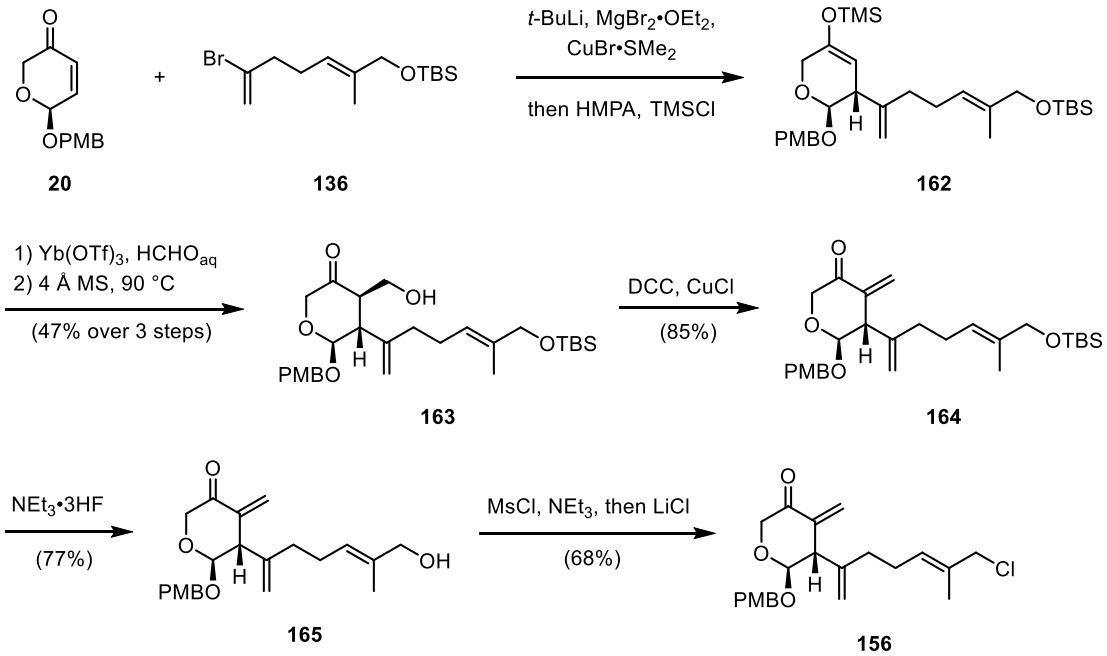
Scheme 43. Proposed radical cyclization for the synthesis of the (*E*)-cyclononene.

The radical cyclization precursor should be readily accessible by employing a similar synthetic strategy as before. The vinyl bromide building block was slightly modified, as illustrated in Scheme 44. First, reduction of *tert*-butyl ester **137** with DIBAL-H afforded aldehyde **159**, which was converted to conjugated methyl ester **160** by Wittig olefination. Next, reduction with DIBAL-H, followed by conversion of the generated alcohol **161** to its silyl ether gave vinyl bromide **136** in high yield (Scheme 44).



Scheme 44. Three-step procedure for the synthesis of vinyl bromide **136**.

With gram quantities of vinyl bromide **136** in hand, *β*-hydroxy ketone **163** could be prepared by using the previously optimized three-step procedure (Scheme 45). The following elimination of the primary alcohol was best achieved by treatment of **163** with dicyclohexylcarbodiimide (DCC) in the presence of copper(I) chloride.[92] The direct introduction of the conjugated *exo*-methylene group was also investigated by reaction of TMS enol ether **162** with Eschenmoser's salt (dimethylmethylideneammonium iodide)[93] (not shown). However, the reaction afforded a mixture of different unidentified products. Thus, the sequence shown in Scheme 45 was used for the preparation of enone **164**. Deprotection of the silyl ether with triethylamine trihydrofluoride and chlorination of the allylic alcohol finally afforded allylic chloride **156**.

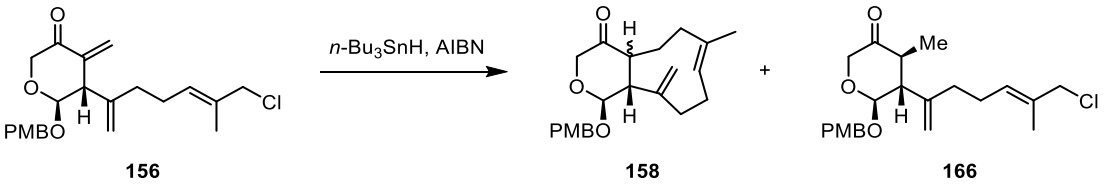


Scheme 45. Preparation of enone **156**.

With substrate **156** in hand, the free radical cyclization was investigated (Table 13). The initial attempt to convert enone **156** to bicycle **158** in the presence of *n*-Bu_3SnH and AIBN at 80 °C was

discouraging and resulted in decomposition (entry 1). Next, a solution of *n*-Bu_3SnH/AIBN was added dropwise via syringe pump which led to the isolation of reduction product **166** in low yield (entry 2). This result implied that palladium impurities in the reaction mixture catalyzed a hydrostannylation reaction of enone **156** at the expense of the radical cyclization. This undesired side reaction could be suppressed when the reaction was performed in new glass ware with new stir bars, but only decomposition was observed.

Table 13. Radical cyclization conditions.



156 **158** **166**

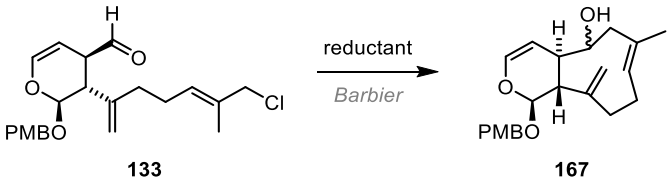
Entry	Conditions[a]	Observation
1[b]	*n*-Bu_3SnH, AIBN	decomposition
2[c]	*n*-Bu_3SnH, AIBN	**166** (27%) + decomposition
3[c,d]	*n*-Bu_3SnH, AIBN	decomposition

[a]All reactions were performed in degassed benzene at 80 °C. [b]The substrate was premixed with the reagents. [c]Slow addition (1 h 20 min) of *n*-Bu_3SnH and AIBN via syringe pump. [d]New glass ware and a new magnetic stir bar were used.

As attempts for the free radical cyclization of enone **156** gave only unsatisfactory results, we decided to base our investigations on more stable key step precursors.

3.4.5 Barbier Reaction

Another popular ring closing method is the Barbier reaction, a nucleophilic addition reaction of halocarbonyl compounds in the presence of reductants (Scheme 46).

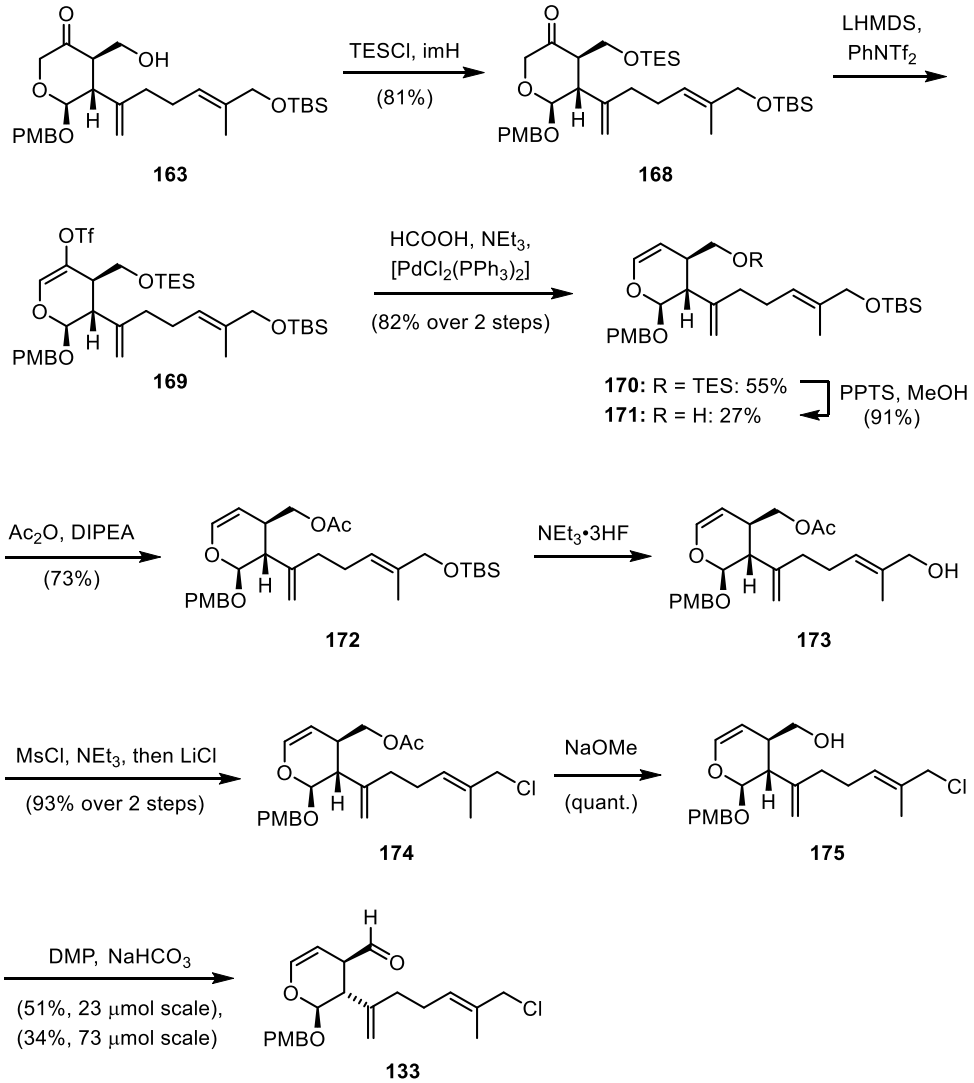


133 **167**

Scheme 46. Attempted Barbier cyclization.

The precursor for this key reaction could be easily accessed from previously prepared *β*-hydroxy ketone **163**. A suitable protecting group needed to be installed to further transform the dihydropyran core. For this purpose, we intended to directly introduce an acetate protecting group, but treatment

of **163** with acetic anhydride in the presence of pyridine resulted in elimination affording an exocyclic methylene group (not shown). Thus, a TES ether was chosen as protecting group and alcohol **168** was subjected to standard silylation conditions (Scheme 47). Treatment of ketone **168** with LHMDS and $PhNTf_2$ afforded vinyl triflate **169**. A palladium-catalyzed reduction of the vinyl triflate to enol ether **170** resulted in partial cleavage of the TES ether and provided a mixture of alcohol **171** and TES ether **170**. The selective deprotection of the TES ether in the presence of the TBS ether with catalytic amounts of pyridinium *para*-toluenesulfonate (PPTS) afforded primary alcohol **171** in high yield, which was converted to acetate **172**. The next steps were based on previously employed conditions to convert the allylic TBS ether to the corresponding allylic chloride, followed by deprotection of the acetate group to afford alcohol **175** in good yields.



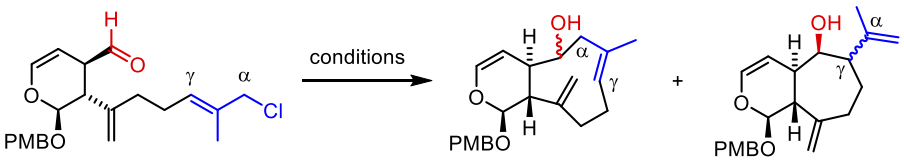
Scheme 47. Preparation of allylic chloride **133**.

Unfortunately, attempted oxidation of the alcohol under Swern conditions[94] resulted in decomposition of the substrate (not shown). Treatment of alcohol **175** with $NaHCO_3$-buffered DMP

afforded the aldehyde in moderate yields, which was found to be highly unstable. Consequently, aldehyde **133** was prepared and then immediately subjected to different Barbier cyclization conditions.

SmI_2-mediated Barbier reactions of halocarbonyl compounds are popular methods for the synthesis of five- to eight-membered rings.[95] Based on these results, our studies on the Barbier cyclization commenced with the use of SmI_2 as the reagent of choice (Table 14). The direct Barbier coupling of aldehyde **133** in the presence of SmI_2 or the SmI_2-HMPA complex resulted in decomposition at 25 °C and in no conversion at −78 °C (entries 1−4). We therefore turned our attention to indium(0)-mediated allylation reactions which have been described to be α-selective when the reaction was performed in water.[96] Thus, aldehyde **133** was treated with indium in a mixture of water and dichloromethane, but no conversion was observed (entry 5). The addition of tetrabutylammonium iodide (TBAI) to the reaction mixture to generate the allylic iodide was also unsuccessful (entry 6). Next, the *in situ* formation of the allylic iodide by treatment of **133** with sodium iodide and subsequent addition of $SnCl_2$[97] cleanly gave alcohol **176** as a diastereomeric mixture, resulting from a 7-*endo-trig* cyclization mode (entry 7). This result was not surprising because γ-allylation reactions are usually favored over α-allylation due to higher stabilization of the generated allyl anion in γ-position.

Table 14. Barbier reaction conditions.



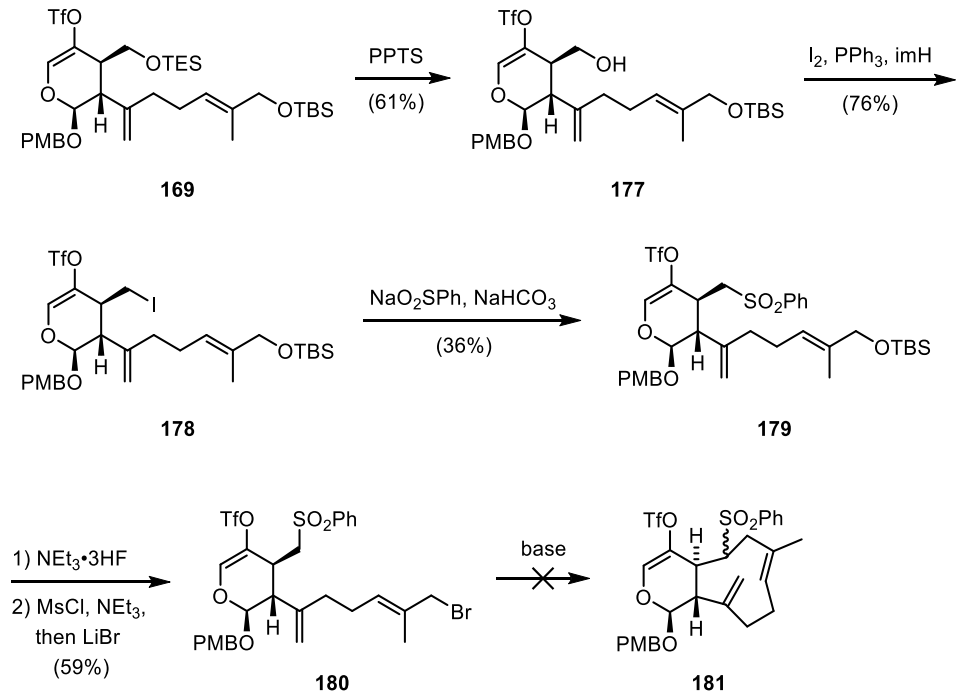
133 **167** **176**

Entry	Conditions	Solvent	T (°C)	Observation
1	SmI_2, HMPA	THF	0	decomposition
2	SmI_2, HMPA	THF	−78	no conversion
3	SmI_2	THF	−78	no conversion
4	SmI_2	THF	25	decomposition
5	In^0	H_2O, CH_2Cl_2	25	no conversion
6	In^0, TBAI	H_2O, CH_2Cl_2	25	no conversion
7	$SnCl_2$, NaI	DMF	25 to 60	**176** (86% yield)

3.4.6 α-Alkylation

As the Barbier reaction was not applicable to the synthesis of the (*E*)-cyclononene fragment, the next synthetic strategy was based on circumventing the undesired γ-allylation. An intramolecular α-alkylation of a sulfone-stabilized carbanion onto an allylic halide was envisaged as key step to construct the cyclononene. Although this strategy has been employed in the past for medium-sized rings, such as eight-,[98] ten-[99] and eleven-membered rings,[100] the use of this reaction for the formation of nine-membered rings is unprecedented.

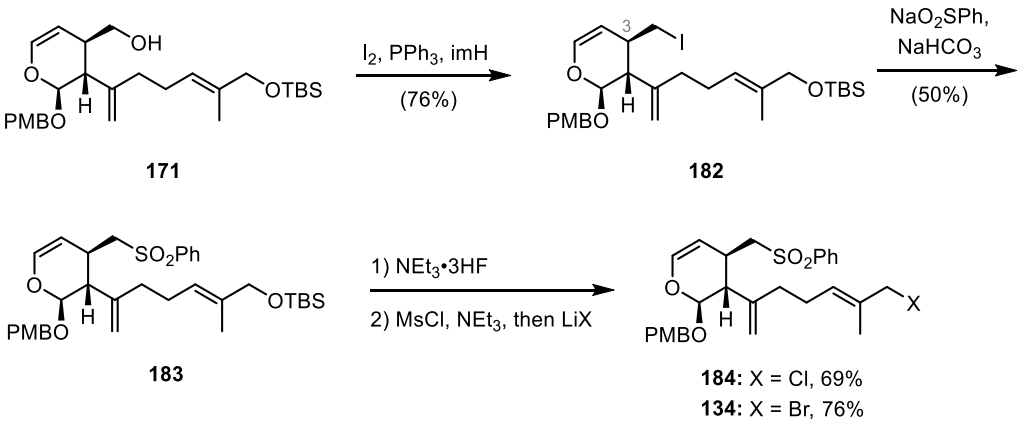
Starting from triflate **169** as a common intermediate, the phenylsulfonyl group was introduced by conversion of alcohol **177** to iodide **178** and by subsequent nucleophilic displacement of the iodide with sodium benzene sulfinate (Scheme 48). To our surprise, the yield of this transformation was unexpectedly low and it was found that a competing elimination reaction generated a diene. All attempts to improve the yield of the nucleophilic displacement product **179** were unsuccessful (e.g. different reaction solvents, temperature and bases) (not shown). While the yield of this transformation was only moderate, the reaction provided ample material to proceed with the synthesis. Deprotection of the silyl ether and mesylation of the generated allylic alcohol gave an allylic mesylate, which was directly subjected to a THF-solution of lithium bromide to afford allylic bromide **180**.



Scheme 48. Preparation of sulfone **180** and attempted α-alkylation.

Next, the intramolecular α-alkylation of sulfone **180** was examined to construct the nine-membered carbocycle. To our disappointment, we were unable to realize this transformation. Treatment of

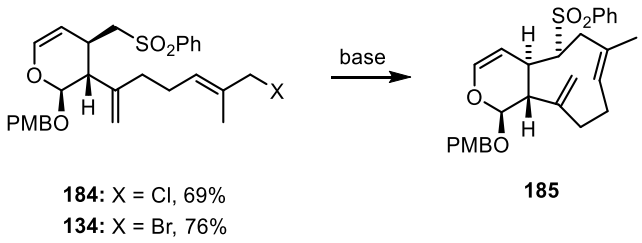
180 with different bases only resulted in the formation of a complex product mixture. We reasoned that the triflate might interfere with the α-alkylation reaction and decided to proceed with an enol ether moiety instead. Thus, alcohol **171** was used as starting material (Scheme 49). By employing the same transformations as described before (see Scheme 48), the sulfone group and the allylic bromide were introduced to afford cyclization precursor **134**. Interestingly, lower C–H acidity at C3 position of enol ether **182** as compared to vinyl triflate **178** resulted in an increased yield for the sulfonylation reaction. We additionally prepared the corresponding allylic chloride **184**.



Scheme 49. Synthesis of sulfones **184** and **134**.

With sulfones **184** and **134** in hand, we proceeded to the investigation of the intramolecular α-alkylation (Table 15).

Table 15. Cyclization of sulfones **184** and **134**.



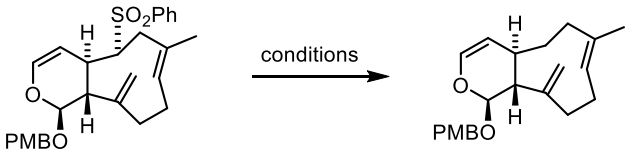
Entry	Substrate	Base, Additive	T (°C)	t (h)	Yield[a]
1[b]	**184**	LHMDS	60	6	10%
2[b]	**184**	KHMDS, 18-crown-6	60	2	0% (decomposition)
3[b]	**134**	KHMDS	0 to 25	1.25	0% (decomposition)
4[c]	**134**	NaHMDS	0	1.25	67%

[a]Isolated yield. [b] Dropwise addition of base to **184** or **134**. [c]Dropwise addition of **134** to base.

First, LHMDS or KHMDS/18-crown-6 were slowly added to a solution of sulfone **184** at 60 °C (entries 1, 2). While 10% yield of bicycle **185** were obtained with LHMDS as base, a complex product mixture was isolated when KHMDS/18-crown-6 was used. When substrate **134** was treated with KHMDS at 0 °C, decomposition was observed (entry 3). Fortunately, slow addition of NaHMDS (4.1 equiv) to **184** at 0 °C afforded bicycle **185** in good yield and as a single diastereomer (entry 4). This example highlights the utility of sulfonyl group for α-regioselective cyclization reactions.

With this successful method for the direct formation of the (*E*)-cyclononene in hand, the next goal in the synthesis of waixenicin A (**11**) was the removal of the phenylsulfonyl group. Several standard conditions for the reductive desulfonylation were employed as shown in Table 16.

Table 16. Screening of desulfonylation conditions.

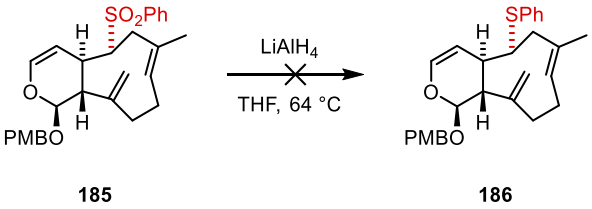


185 **130**

Entry	Conditions	T (°C)	Observation
1	Mg (exess), MeOH	23 to 50	complex mixture
2	Mg (exess), $NiBr_2$, MeOH	23 to 50	no conversion
3	Mg (exess), $HgCl_2$ (cat.), MeOH	23	complex mixture
4	Mg (3.0 equiv), NaH_2PO_4, $HgCl_2$ (cat.), THF, EtOH	23 to 50	no conversion
5	SmI_2, HMPA, *t*-BuOH	–78 to 23	no conversion
6	Al(Hg), THF, H_2O	25 to 50	no conversion
7	Al, $HgCl_2$, MeOH	60	no conversion
8	Na(Hg), NaH_2PO_4, THF, MeOH	23	no conversion
9	Na(Hg) (20 equiv), Na_2HPO_4, MeOH, THF	23	complex mixture
10	Raney-Ni (2800), EtOH	70	complex mixture
11	Raney-Ni (2800), THF	25	complex mixture
12	$NiCl_2 \cdot 6\ H_2O$, $NaBH_4$	25	no conversion
13	Lithium naphthalenide, THF	–78	complex mixture

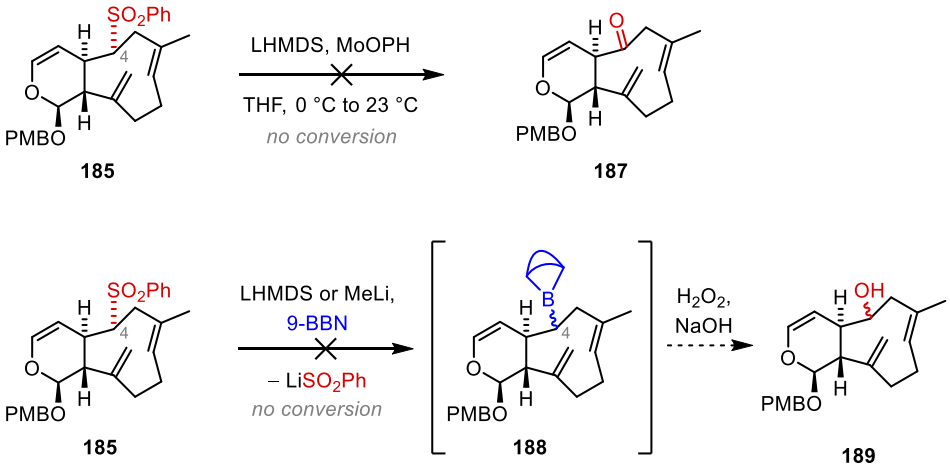
Unfortunately, an extensive screening of reaction conditions for the reductive desulfonylation was unsuccessful and either no conversion or complete decomposition of the starting material was observed. At this point, it remained unclear if the enol ether moiety or a subsequent intramolecular reaction with one of the double bonds of the cyclononene were responsible for the formation of complex product mixtures.

Further attempts to reduce sulfone **185** to the corresponding sulfide also proved to be unsuccessful (Scheme 50).



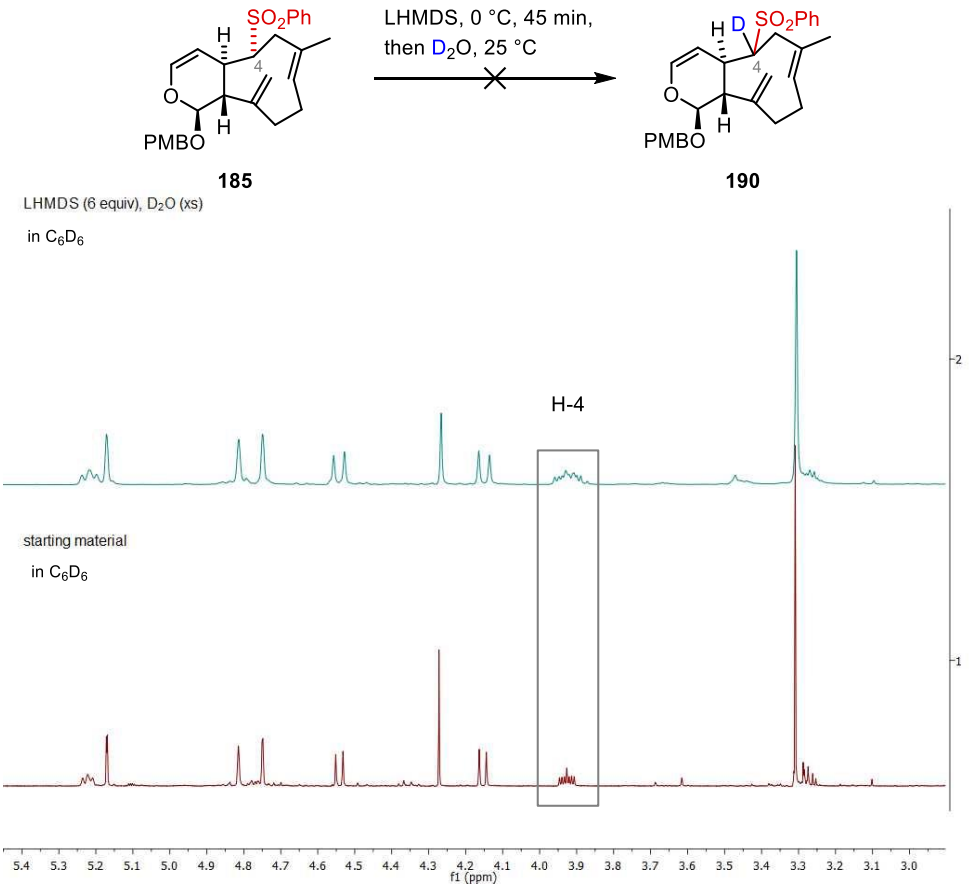
Scheme 50. Attempted reduction of sulfone **185**.

Given the difficulties encountered with the reductive desulfonylation of **185**, we next investigated the oxidation of the alkyl sulfone to the corresponding ketone **187** or alcohol **189** (Scheme 51).[101]



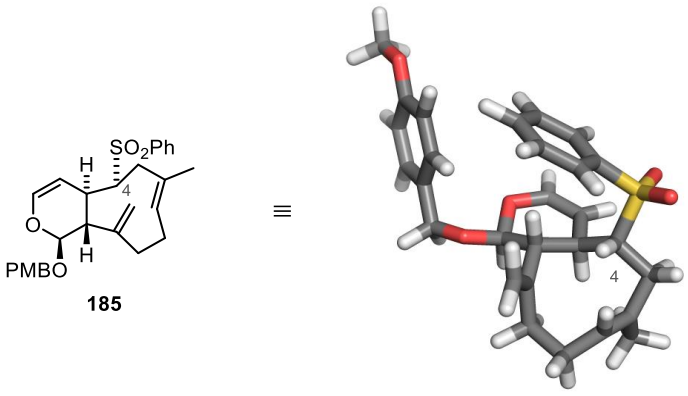
Scheme 51. Attempted oxidation of sulfone **185** (MoOPH = oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)).

Since none of the reactions resulted in consumption of the starting material **185**, it was examined if the deprotonation at C4 position was feasible. Thus, sulfone **185** was treated with LHMDS (6 equiv) at 0 °C for 45 min before an excess of deuterium oxide was added. NMR studies revealed that no deuterium incorporation at C4 position took place (Scheme 52).



Scheme 52. Deuterium incorporation experiment.

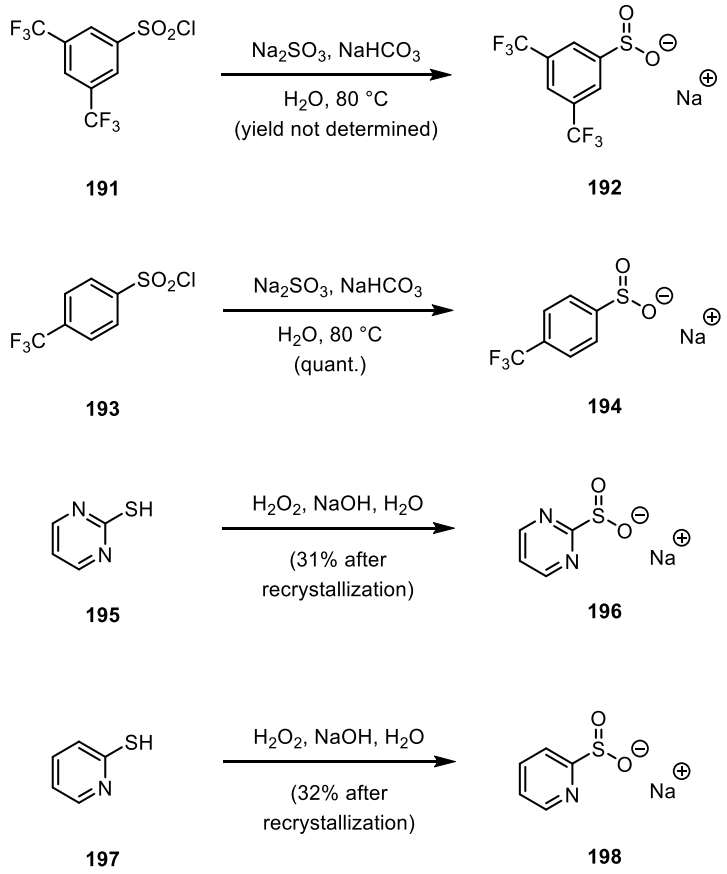
We reasoned that the general sterical hindrance in the nine-membered ring prevented deprotonation of the methine proton at C4 position. This explanation was substantialized by the optimized structure of sulfone **185** at the ωB97X-D/6-31G* computational level of theory, which further demonstrated the sterically challenging environment of the proton (Scheme 53).



Scheme 53. DFT-optimized molecular structure of bicycle **185**.

Another strategy to remove the sulfonyl group was based on the change of the electronic properties of the aryl group. We reasoned that the introduction of more electron-deficient aryl substituents

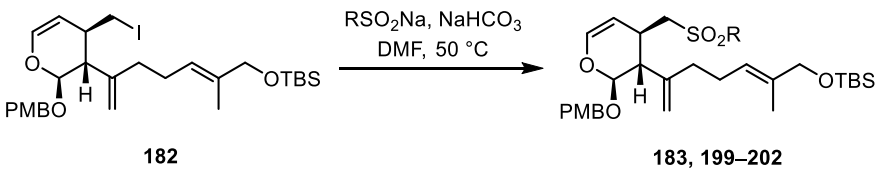
would facilitate reductive cleavage of the sulfonyl group and would allow for the use of milder conditions. Thus, the preparation of a series of electron-deficient sulfinate salts was examined. In general, sodium aryl sulfinates can be either prepared by reduction of the corresponding aryl sulfonyl chlorides[102] or by oxidation of the corresponding aryl thiols under basic conditions.[103] The first strategy was applied for the syntheses of sodium 4-(trifluoromethyl)benzene sulfinate (**192**) and sodium 3,5-bis(trifluoromethyl)benzene sulfinate (**194**). The corresponding pyridine and pyrimidine sulfinate salts **196** and **198** were prepared by oxidation with hydrogen peroxide (Scheme 54).



Scheme 54. Preparation of different sodium arylsulfinates.

While none of the reactions resulted in selective formation of the sulfinate salts, tedious purification by recrystallization from ethanol was necessary to obtain pure material. To our surprise, when iodide **182** was reacted with the different sulfinate salts **192**, **194**, **196** and **198** using the previously optimized reaction conditions, the corresponding elimination product was always obtained as the major, if not the only, product (Table 17). The installation of electron-withdrawing substituents on the aryl moiety apparently had a dramatic effect on the nucleophilicity of the sulfinate salts.

Table 17. Introduction of different sulfones.



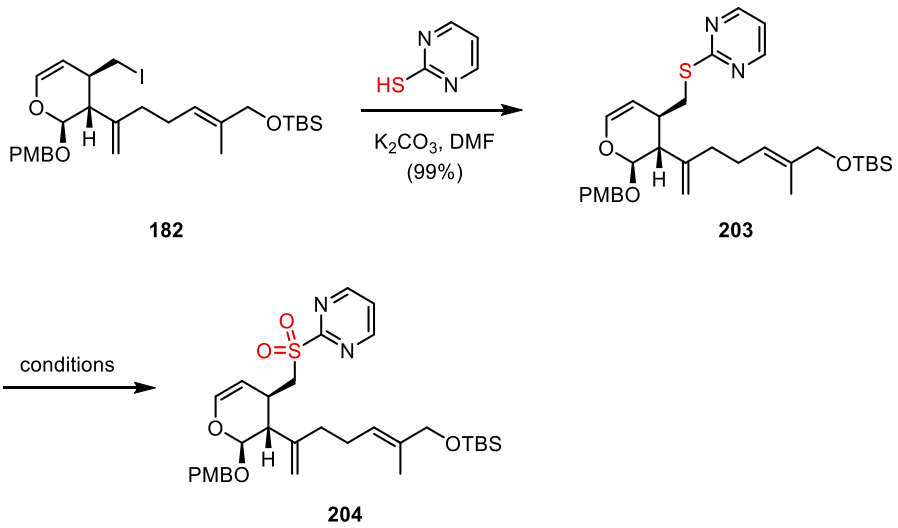
182 **183, 199–202**

Entry	R	Product	Yield[a]
1	Ph	**183**	45–50%
2	3,5-$(CF_3)_2$-C_6H_3	**199**	0%
3	4-CF_3-C_6H_4	**200**	23%
4	pyrimidine	**201**	0%[b]
5	pyridine	**202**	16%

[a]Isolated yield. [b]The reaction was also performed in MeCN at 25 °C and 50 °C, but no yield improvement was observed.

Given these results, we decided to abandon this strategy and examined the oxidation of the corresponding sulfides instead. By contrast to the nucleophilic substitution with sulfinate salts, the synthesis of the sulfides from primary iodide **182** gave the products in high yields and no competing elimination reaction was observed. Pyrimidine sulfide **203** was chosen as substrate for a screening of different oxidation conditions (Table 18). While the use of *m*-CPBA, magnesium monoperoxyphthalate (MMPP) and ammonium molybdate/hydrogen peroxide[104] resulted in the formation of complex product mixtures (entries 1−4), no reaction was observed when manganese sulfate/hydrogen peroxide[105] or TPAP/NMO[106] were used (entries 5, 6).

Table 18. Screening of oxidation conditions for sulfide **203**.



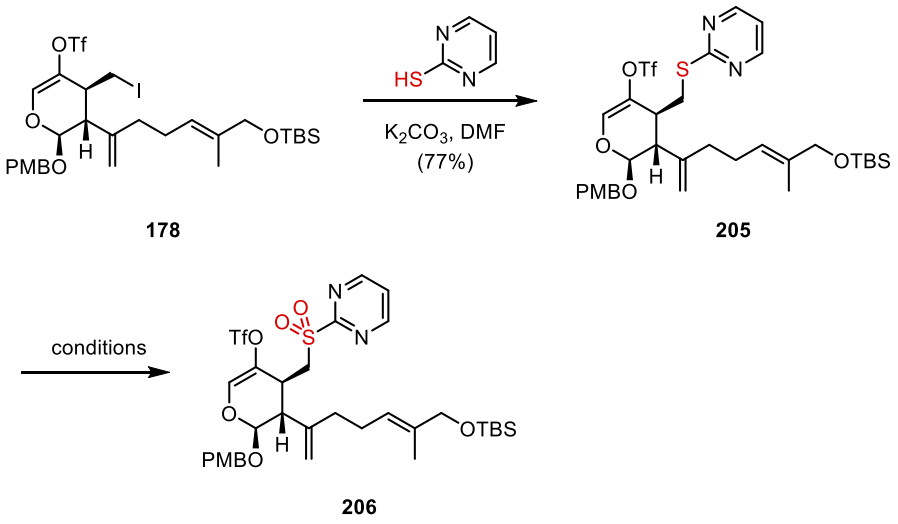
182 **203** **204**

Entry	Oxidant(s)	Solvent	T (°C)	Yield
1	*m*-CPBA	CH_2Cl_2	0	0%
2	*m*-CPBA	CH_2Cl_2	−30	0%
3	silica supported MMPP	CH_2Cl_2	40	0%
4	H_2O_2, $(NH_4)_6Mo_7O_{24}$	EtOH	25	0%
5	H_2O_2, $MnSO_4 \cdot H_2O$	MeCN	25	0%
6	TPAP, NMO, 4 Å MS	MeCN	25	0%

[a]Isolated yield. (MMPP = magnesium monoperoxyphthalate, TPAP = tetrapropylammonium perruthenate).

We reasoned that the electron-rich C−C double bond of the enol ether is very susceptible to attack by electrophiles and thus decided to use vinyl triflate **178** instead (Table 19). While the use of *m*-CPBA as oxidant resulted both in oxidation of the sulfide to the sulfoxide and in epoxidation of the trisubstituted double bond (entry 1), the use of sodium tungstate/hydrogen peroxide[107] (entry 2) resulted in no conversion. In constrast, an ammonium molybdate catalyzed hydrogen peroxide oxidation procedure gave low amounts of the product, when 10 mol% of the catalyst was employed (entry 3). When 50 mol% of the catalyst were used, the reaction afforded sulfone **206** in 21% yield on a 28 mg scale (entry 4). To our surprise, the yield was increased to 94%, when the reaction was performed with 15 mol% catalyst on a 13 mg scale (entry 5). However, all attempts to repeat this result by employing between 10 and 20 mol% of the catalyst only gave inconsistent results and this route was therefore not further pursued.

Table 19. Screening of oxidation conditions for sulfide **205**.



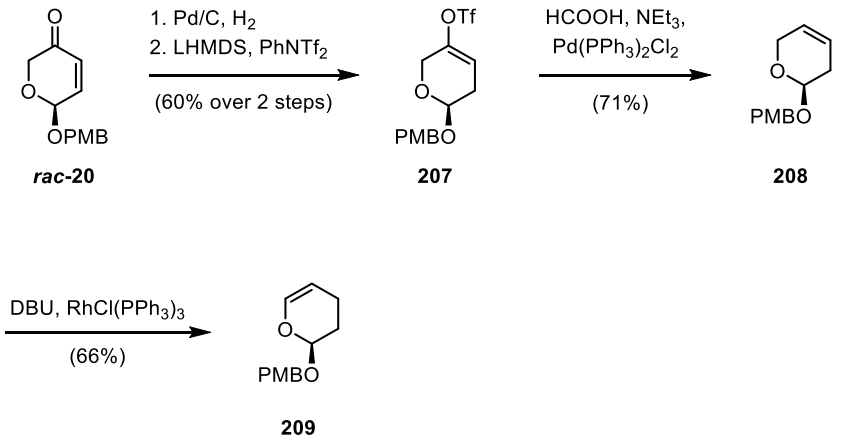
178 **205** **206**

Entry	Oxidant(s)	Solvent	T (°C)	Yield[a]
1	*m*-CPBA	CH_2Cl_2	0	0%
2	H_2O_2, $Na_2WO_4 \cdot 2\ H_2O$	EtOAc, H_2O	25	0%
3	H_2O_2, $(NH_4)_6Mo_7O_{24}$	EtOH	25	~10%[b]
4	H_2O_2, $(NH_4)_6Mo_7O_{24}$	EtOH	25	21%[c]
5	H_2O_2, $(NH_4)_6Mo_7O_{24}$	EtOH	25	94%[d]

[a]Isolated yield. [b]10 mol% of the catalyst were used. [c]50 mol% of the catalyst were used. [d]15 mol% of the catalyst were used.

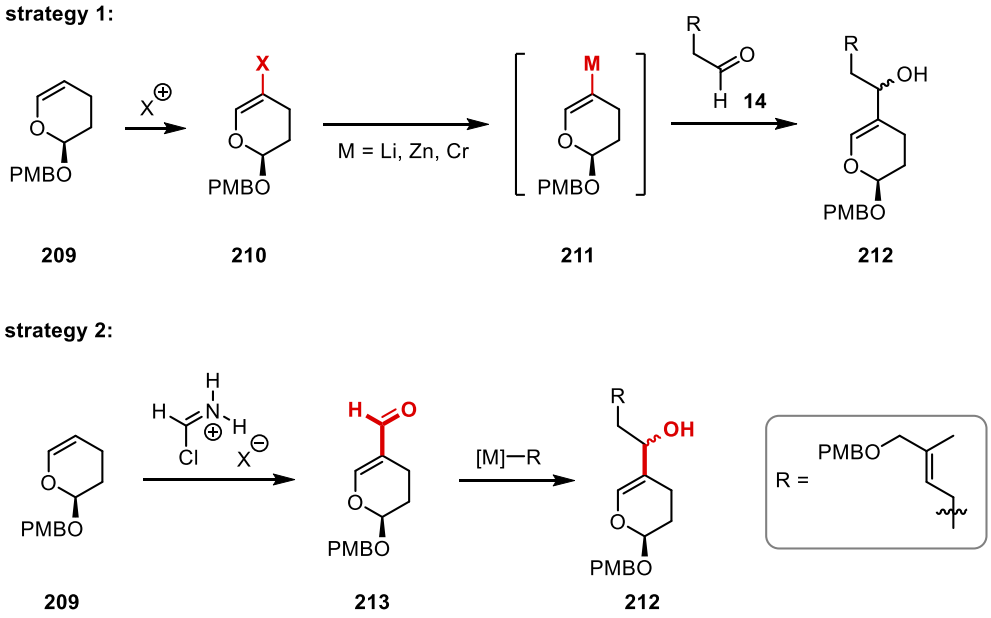
3.4.7 Side Chain Introduction

Due to these unsuccessful results, we abandoned these investigations at this stage to further explore the introduction of the side chain of the natural product by functionalization of the enol ether. We reasoned that a higher substitution of the enol ether would lead to an enhanced stability of this base and acid labile group for desulfonylation reactions. Therefore, model substrate **209** was efficiently prepared in four steps from racemic enone **20** (Scheme 55).



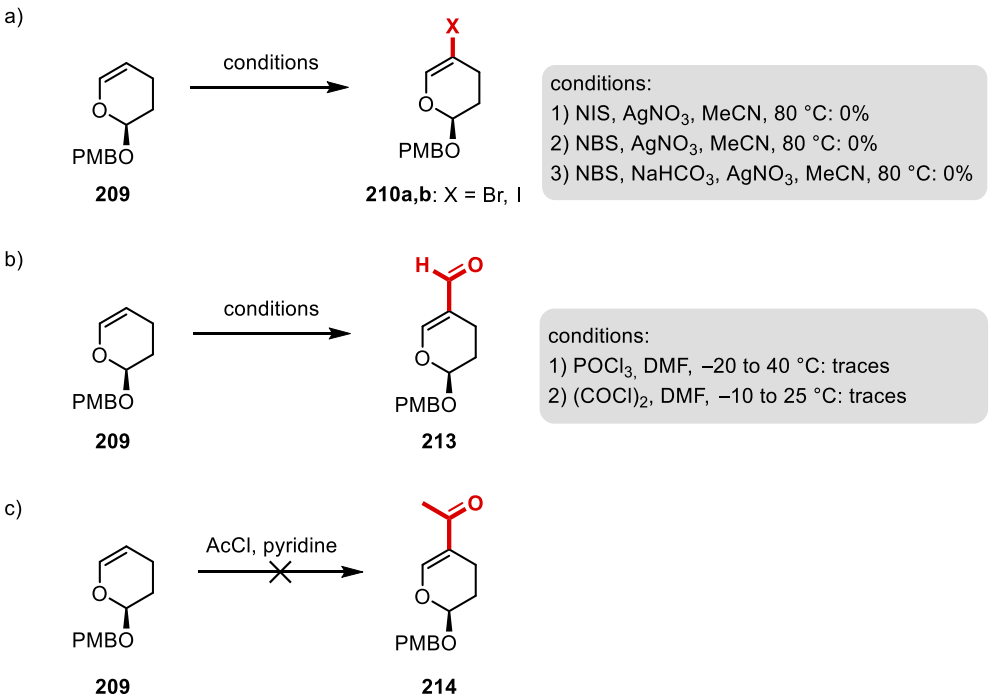
Scheme 55. Preparation of model substrate **209**.

In general, we envisioned two different strategies for the introduction of the side chain (Scheme 56). First, a coupling of the corresponding vinylic organometallic species **211** with known aldehyde **14** and second, allylation of *α,β*-unsaturated aldehyde **213**.



Scheme 56. Two different strategies for the introduction of the side chain.

With model substrate **209** in hand, the halogenation of the enol ether was examined first. Treatment of **209** with NIS or NBS and silver nitrate[108] in the presence or absence of $NaHCO_3$ as buffer resulted in full decomposition of the starting material (Scheme 57a).

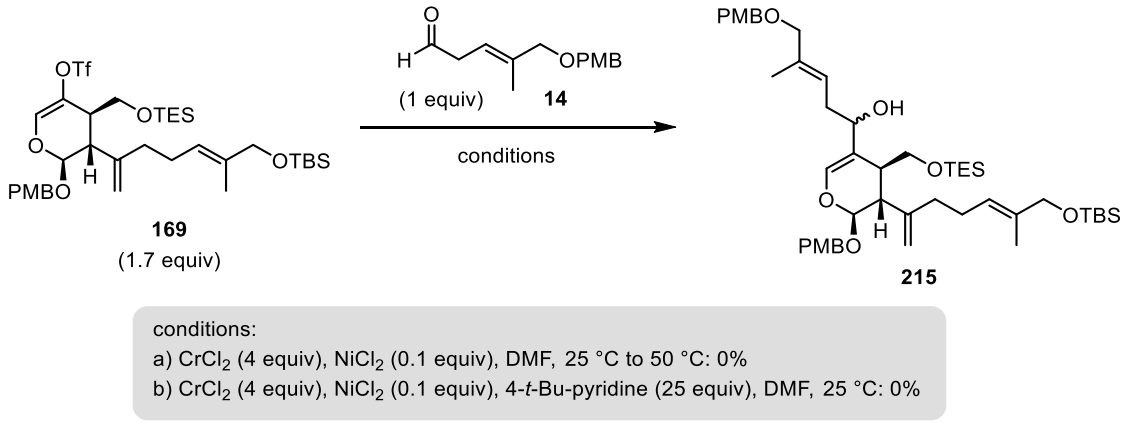


Scheme 57. Attempted (a) halogenation, (b) formylation and (c) acylation of enol ether **209**.

Next, enol ether **209** was subjected to the Vilsmeier reagent, prepared from either $POCl_3$/DMF or $(COCl)_2$/DMF. While trace amounts of the desired aldehyde were observed by ^1H NMR

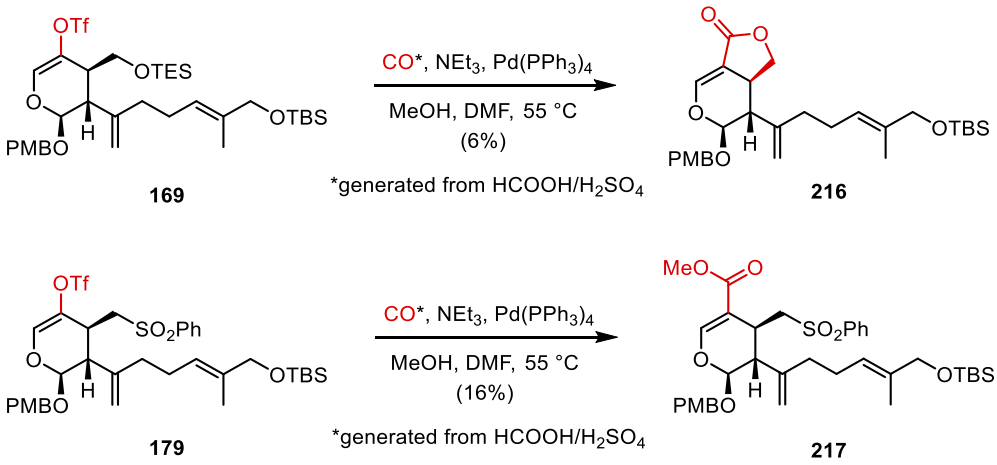
spectroscopy, the product could not be isolated (Scheme 57b). Vilsmeier acylation with acetyl chloride as a model substrate for the side chain was also unsuccessful (Scheme 57c).

Given these difficulties encountered with the functionalization of the enol ether, we set out to functionalize the vinyl triflate at an early stage of the total synthesis. Our first idea for the introduction of the side chain was the reductive coupling between triflate **169** and literature-known aldehyde **14**[38] (Scheme 58). However, treatment of aldehyde **14** and vinyl triflate **169** with an excess of chromium(II) chloride and catalytic amounts of nickel(II) chloride resulted in no conversion. It was assumed that the low reactivity of the triflate hampered a successful reaction. The use of 4-*tert*-butyl pyridine as additive has been described to generally enhance the reaction rate by dissolving solid chromium(II) salts and by suppressing homo coupling reactions. With the addition of 4-*tert*-butyl pyridine, vinyl triflates have been found to show good reactivity under NHK conditions.[109] However, no conversion was observed when 4-*tert*-butyl pyridine was added to the NHK reaction mixture of aldehyde **14** and vinyl triflate **169**.



Scheme 58. Attempted NHK coupling.

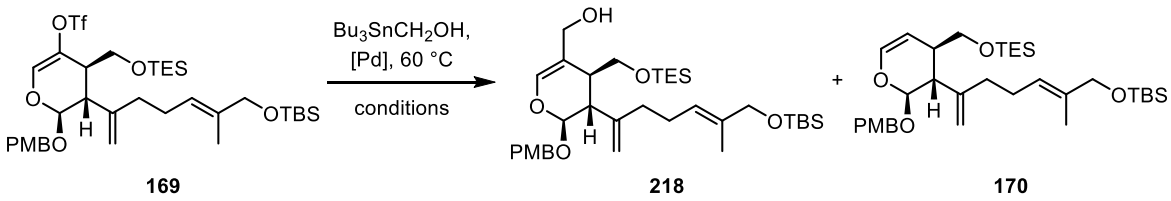
Our next synthetic strategy was based on the conversion of the triflate to the corresponding *α,β*-unsaturated aldehyde. The aldehyde should then later be functionalized by Mukaiyama aldol reaction or by asymmetric allylation to install the side chain of the natural product. Initial studies for the introduction of the aldehyde were directed to palladium-catalyzed carbonylation reactions (Scheme 59). In a first attempt, the TES protecting group of triflate **169** was found to be unstable under these conditions and only trace amounts of lactone **216** could be isolated. Thus, the reaction was repeated by using sulfone **179** instead, but the yield could only be slightly improved.



Scheme 59. Palladium-catalyzed carbonylation reactions.

Next, palladium-catalyzed hydroxymethenylation of triflate **169** with Bu_3SnCH_2OH under Stille conditions was examined (Table 20). In a first attempt, reduction product **170** was obtained as major product (43% yield) together with the desired alcohol **218** (23% yield, entry 1). By changing the solvent from THF to 1,4-dioxane the yield increased to 47% after 2 h at 60 °C (entry 2). The use of $Pd(dba)_2$, P(*o*-fur)$_3$ and $ZnCl_2$ in THF at 60 °C resulted in decomposition (entry 3).

Table 20. Stille conditions.

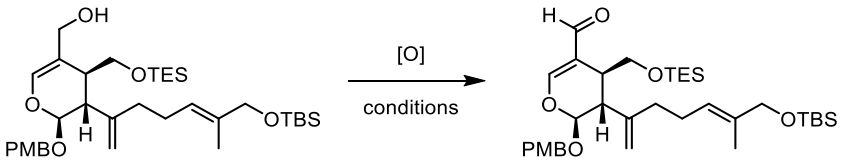


Entry	Conditions	Solvent	Yield[a]
1	$Pd(PPh_3)_4$, LiCl	THF	**218** (23%), **170** (43%)
2	$Pd(PPh_3)_4$, LiCl	1,4-dioxane	**218** (47%), **170** (17%)
3	$Pd(dba)_2$, P(*o*-fur)$_3$, $ZnCl_2$	1,4-dioxane	decomposition

[a]Isolated yield.

With alcohol **218** in hand, oxidation to the aldehyde was investigated (Table 21). Initially, treatment of alcohol **218** with DMP or activated manganese dioxide resulted in no product formation (entries 1, 2). The use of Ley–Griffith oxidation conditions[110] (TPAP, NMO) finally gave aldehyde **219** in good yields (entry 3).

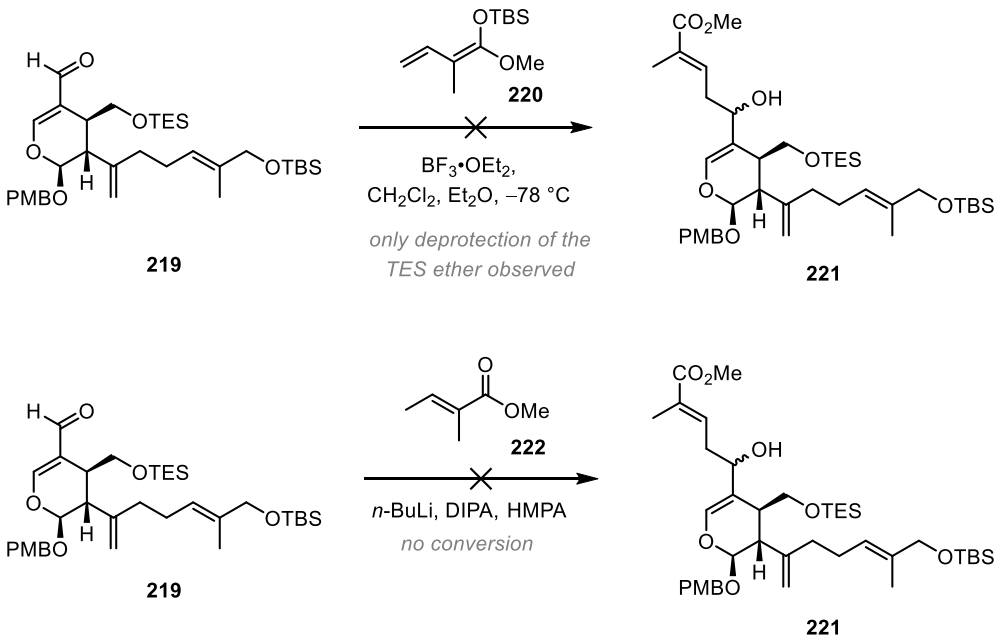
Table 21. Oxidation conditions.



218 **219**

Entry	Conditions	Observation
1	DMP, $NaHCO_3$	complex mixture
2	MnO_2	no conversion
3	NMO, TPAP, 4 Å MS	**219**: 58% yield

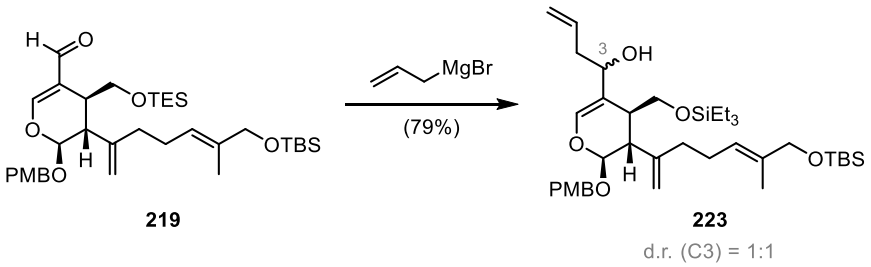
Starting from aldehyde **219**, different ways for the introduction of the side chain were examined. First, a boron trifluoride-mediated Mukaiyama aldol reaction of literature-known TBS ketene acetal **220**[111] with aldehyde **219** should afford alcohol **221**, but the TES ether was deprotected under these conditions (Scheme 60). Next, treatment of **219** with the lithium enolate of tiglic acid methyl ester (**222**) in the presence of HMPA should give the product under milder conditions, but no conversion was observed.



Scheme 60. Unsuccessful introduction of the side chain by Mukaiyama aldol reaction or by addition of a lithium enolate.

Given these difficulties with the functionalization of aldehyde **219**, an allylation/olefin cross metathesis sequence was pursued. Introduction of the ally group by reaction of aldehyde **219** with

ally magnesium bromide afforded alcohol **223** as a mixture of diastereomers (d.r. = 1:1) (Scheme 61).

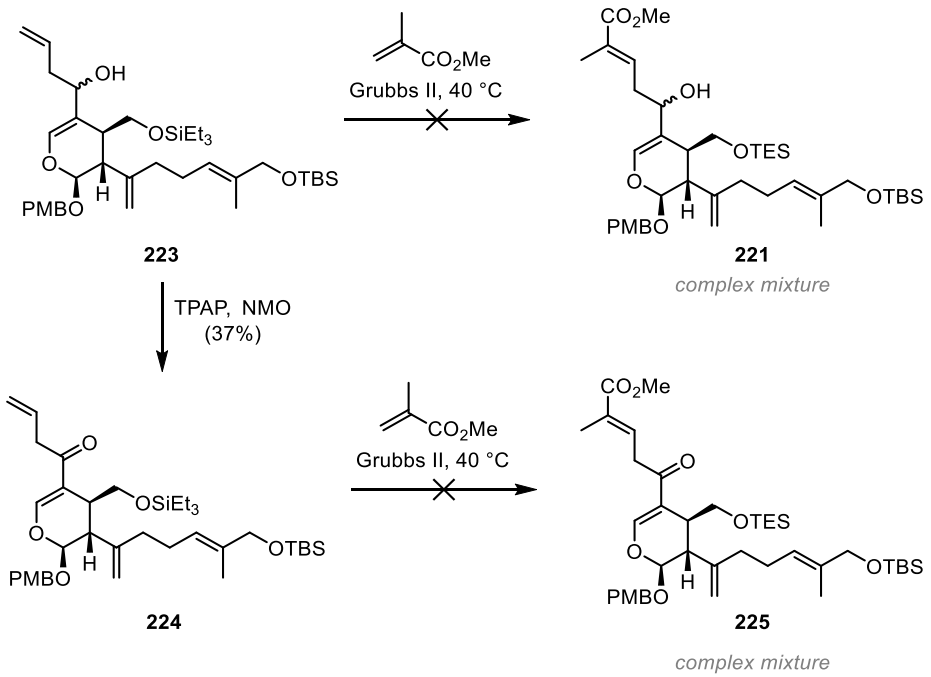


219 **223**

d.r. (C3) = 1:1

Scheme 61. Reaction of aldehyde **219** with allyl magnesium bromide.

Olefin cross metathesis of the terminal alkene with a large excess of methyl methacrylate (30 equivalents) should then introduce the upper part of the side chain, but the formation of a complex product mixture was observed instead (Scheme 62). To verify if the free allylic hydroxyl group of **223** could be responsible for this observation, alcohol **223** was oxidized to ketone **224**. The allylic ketone was then directly subjected to the previously employed olefin cross metathesis conditions. Again, a complex product mixture was obtained.



223 **221**

complex mixture

224 **225**

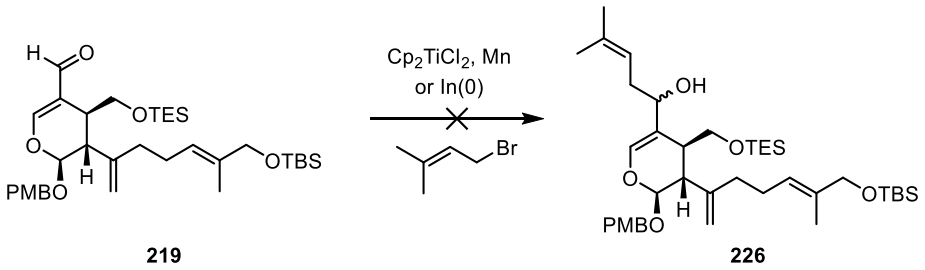
complex mixture

Scheme 62. Unsuccessful allylation/olefin metathesis strategy.

The control of regioselectivity appeared to be a major problem in this reaction. In general, *α,β*-unsaturated esters are excellent cross metathesis partners with terminal alkenes.[112] The choice of catalyst could be crucial for a regio- and stereoselective olefin cross metathesis of the terminal

alkene with methyl methacrylate. Future studies should therefore be focused on the screening of different cross metathesis catalysts.

Following a different idea, the introduction of a higher substituted allyl group was examined by using 3,3-dimethylallyl bromide as model substrate. Certain titanium(III)[113]- or indium(0)-mediated[96] allylation reaction are known to proceed with high α-regioselectivity and were therefore the methods of choice for the allylation of aldehyde **219**. To our surprise, no conversion was observed under both conditions (Scheme 63).



219 **226**

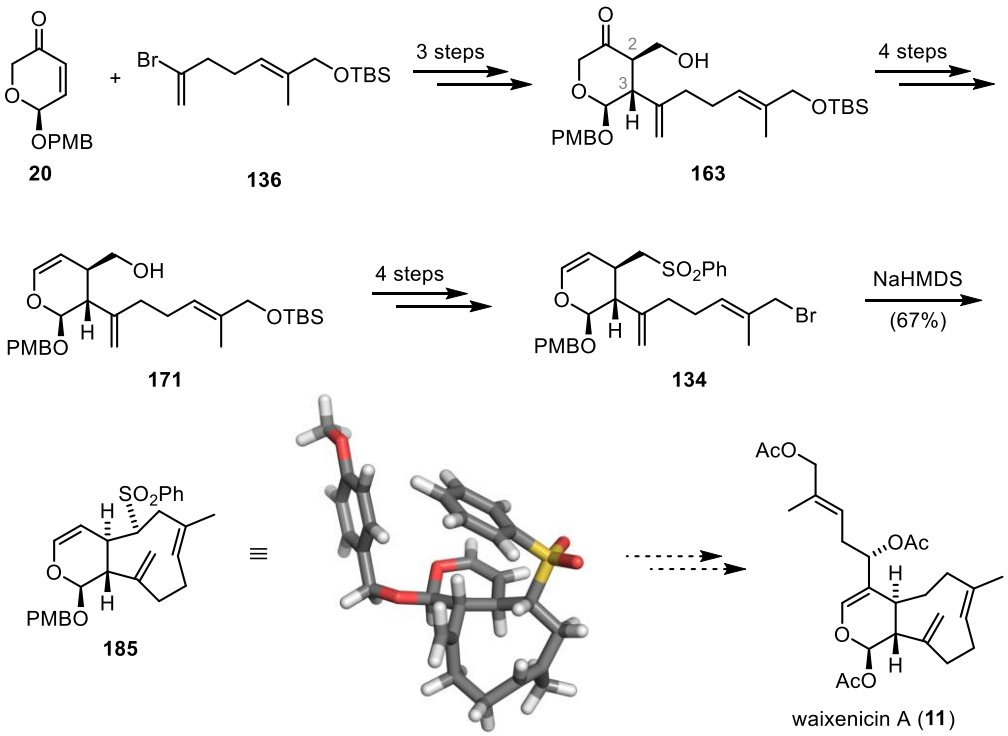
Scheme 63. Attempted α-allylation reactions.

Further studies on the introduction of the side chain are currently under investigation in our laboratory.

4 Summary and Outlook

Progress toward the total synthesis of the *Xenia* diterpenoid waixenicin A (**11**) has been detailed in this thesis. At first, the characteristic (*E*)-cyclononene fragment has been constructed by employing a Grob fragmentation strategy. However, the installation of the dihydropyran ring *trans*-fused to the (*E*)-cyclononene was found to be challenging with this synthetic strategy. Thus, the direct synthesis of the nine-membered ring from acyclic precursors has been studied in detail. These studies resulted in the development of an enantioselective and versatile route for the synthesis of the core structure of the natural product.

Starting from enantiomerically pure enone **20** and readily available vinyl bromide **136**, we prepared *β*-hydroxy ketone **163** in three steps by diastereoselective cuprate addition, trapping of the generated enolate as its TMS enol ether and subsequent Mukaiyama aldol reaction with formaldehyde (Scheme 64).

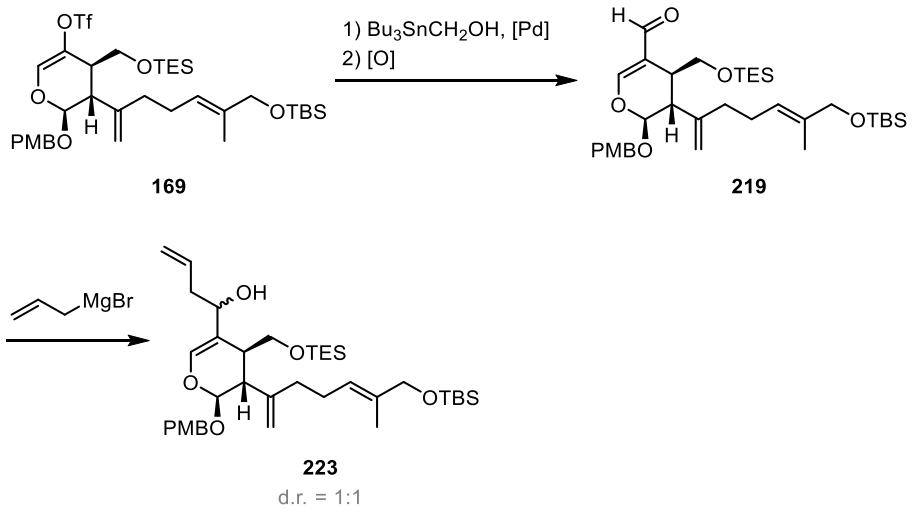


Scheme 64. Convergent asymmetric synthesis of the core structure of waixenicin A (**11**) and DFT-optimized structure of sulfone **185.**

In this transformation, the stereocenter of the acetal group directed the formation of the two contiguous stereocenters at C2 and C3. Subsequent introduction of the enol ether motif was achieved by triflation of the ketone and reduction of the resultant vinyl triflate to alkene **171**. In four additional steps, the phenylsulfonyl group and the allylic bromide were introduced. The challenging cyclization to form the (*E*)-cyclononene fragment was successfully achieved by a

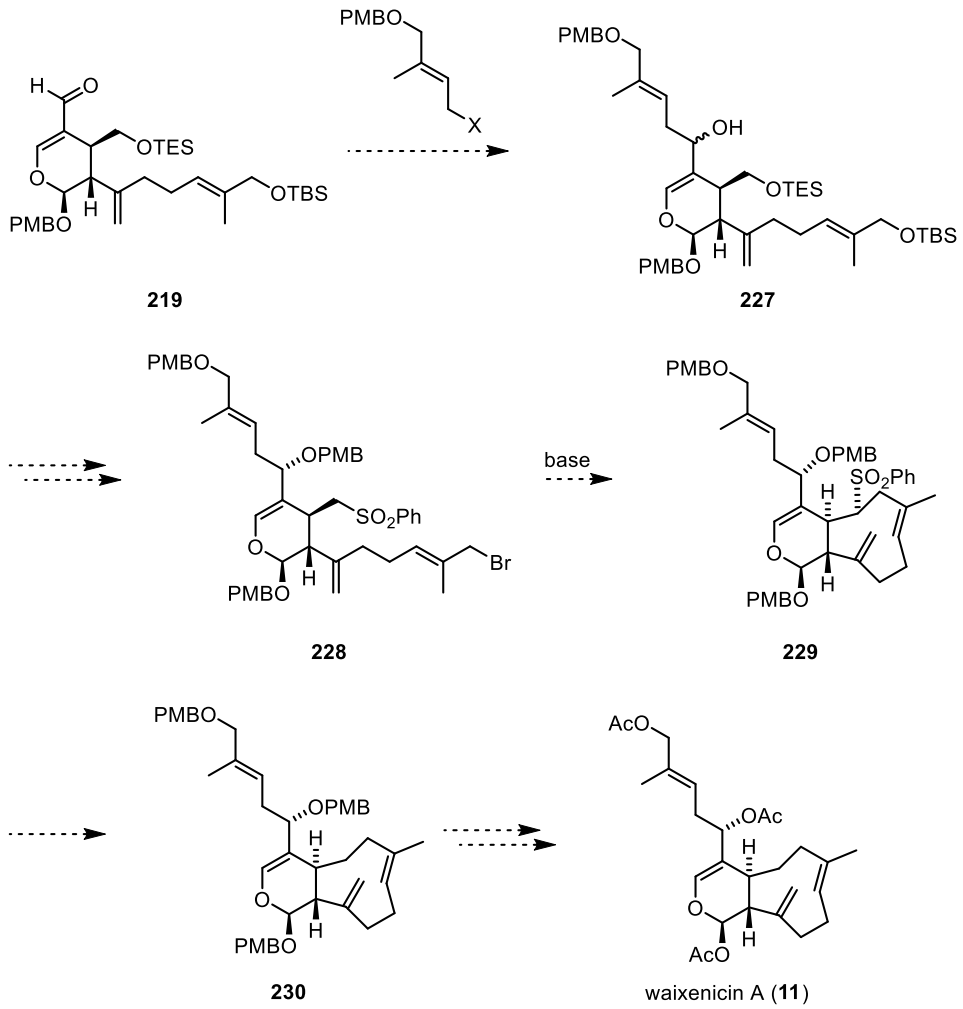
sulfonyl-anion mediated α-alkylation. It is noteworthy that the cyclization resulted in the formation of sulfone **185** as a single diastereomer.

With an established route toward the core structure of the natural product in hand, we extensively investigated conditions for the reductive desulfonylation of the phenylsulfonyl group of **185**. As sulfone **185** proved to be challenging to reduce under several conditions, we resorted to introduce the side chain of waixenicin A (**11**) prior to the key cyclization to enhance the stability of the enol ether motif. In initial experiments, we succeeded in transforming the vinyl triflate **169** to aldehyde **219** (Scheme 65). The introduction of an allyl group has also been established and future studies should be directed to the introduction of the allylic fragment of the side chain of the natural product.



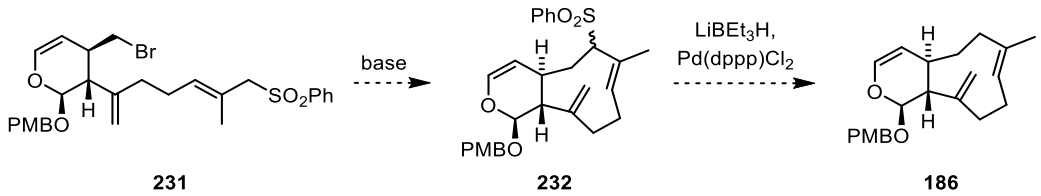
Scheme 65. Functionalization of triflate **169**.

Afterwards, the substrate should be further transformed to allylic bromide **228**. The intramolecular base-mediated α-alkylation using previously established conditions should then afford sulfonyl-waixenicin A analog **229**, which should be subjected to late-stage desulfonylation conditions (Scheme 66).



Scheme 66. Synthesis of sulfonyl-waixenicin A analog **229** en route to waixenicin A (**11**).

In an alternative approach, allylic sulfone **231** should be prepared and the realization of an intramolecular α-alkylation reaction should be investigated. The resulting sulfone **232** could then be reduced using significantly milder desulfonylation conditions, e.g. lithium triethylborohydride/Pd(dppp)Cl_2 (Scheme 67).



Scheme 67. Envisioned synthesis of allylic sulfone **232** and palladium-catalyzed reduction of the sulfonyl group.

Overall, the pursued strategies presented in this thesis constitute significant progress toward the first total synthesis of waixenicin A (**11**) or any member of the xenicin subfamily of natural products. The developed convergent and asymmetric route to the bicyclic core structure of

waixenicin A (**11**) provides a basis for further efforts toward these structurally unique natural products. Further studies on the completion of the total synthesis of waixenicin A (**11**) are currently under investigation in the Magauer laboratories.

PART II

Studies Toward the Total Synthesis of Jerantinine E

5 Introduction

5.1 Monoterpene Indole Alkaloids

Monoterpene indole alkaloids are one the largest classes of alkaloids, comprising over 2000 members.[114] The individual compounds are mainly derived from plants of three families: *Rubiaceae*, *Loganiaceae* and *Apocynaceae*. Some representative members of this class of natural products and their biological functions are shown in Figure 6. Many members of the monoterpene indole alkaloids exhibit promising biological effects including anti-cancer (e.g. vinblastine (**233**), brucine (**235**)), anti-malarial, anti-hypertensive (e.g. ajmalicine (**234**)) or insecticidal (e.g. aspidophytine (**236**)) activities. For decades, these remarkable biological features and their interesting structural complexity rendered these alkaloids attractive targets for synthetic and medicinal chemists.

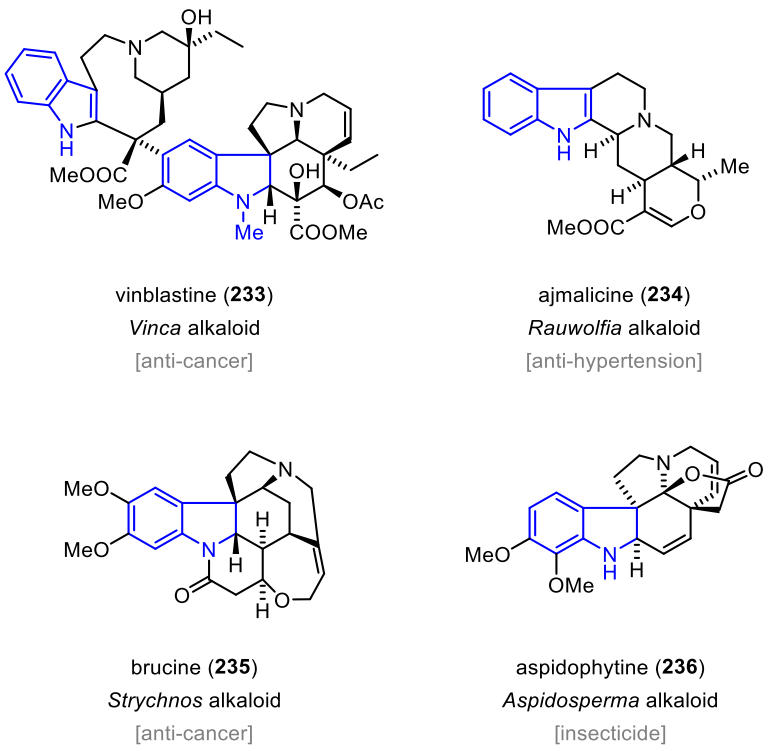
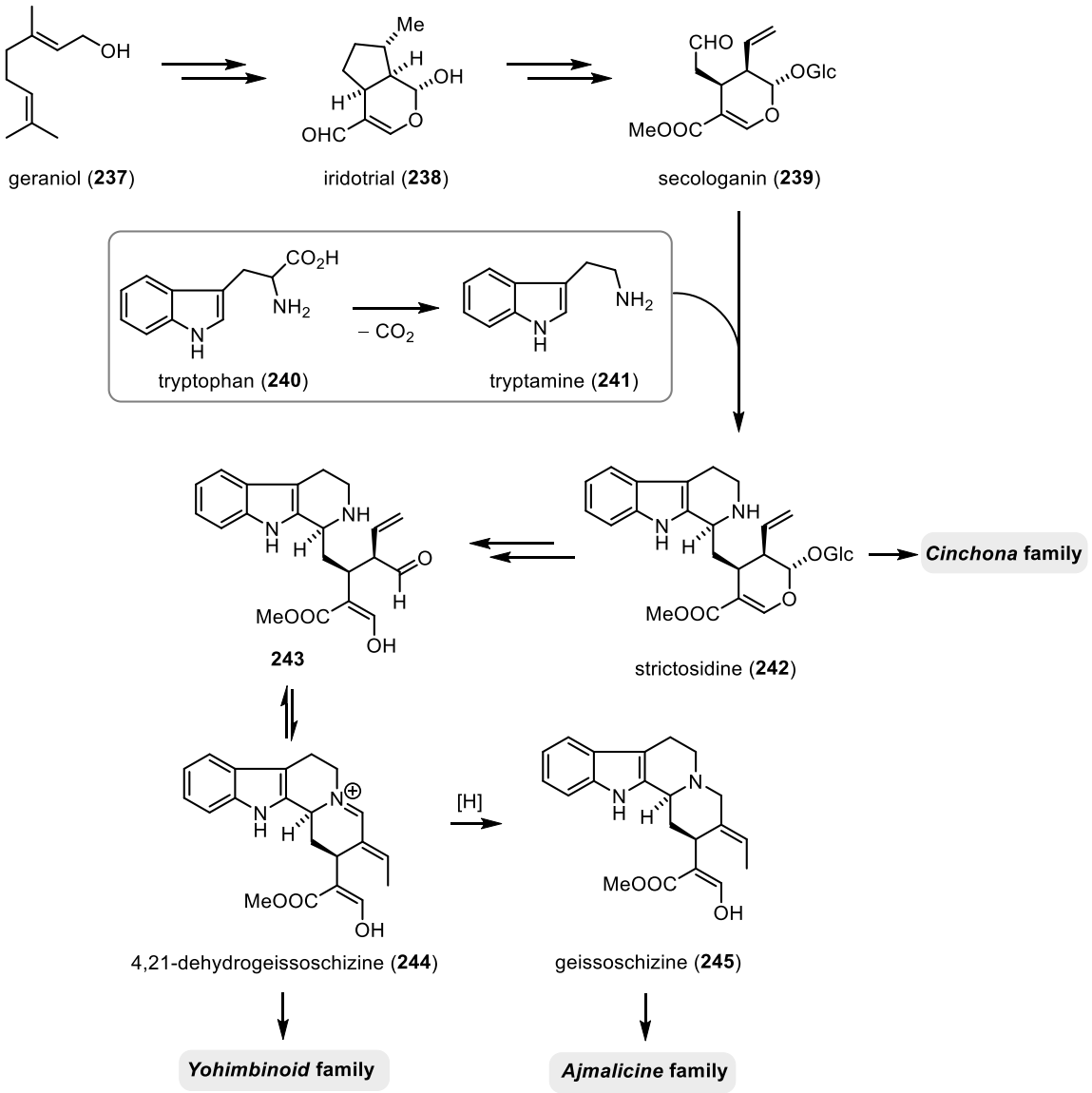


Figure 6. Representative members of the monoterpene indole alkaloid family and their biological features. The indole subunits are highlight in blue

5.2 Biosynthesis of Monoterpene Indole Alkaloids

Monoterpene indole alkaloids are biosynthetically derived from two building blocks: secologanin (**239**) and tryptamine (**241**).[114,115] Secologanin (**239**) itself is a natural product derived from the monoterpene geraniol (**237**).[116–118] Tryptamine (**241**) is obtained by an enzymatic decarboxylation of tryptophan (**240**).[119] In the first step of the biosynthesis, an enzymatic Pictet–Spengler reaction[120]

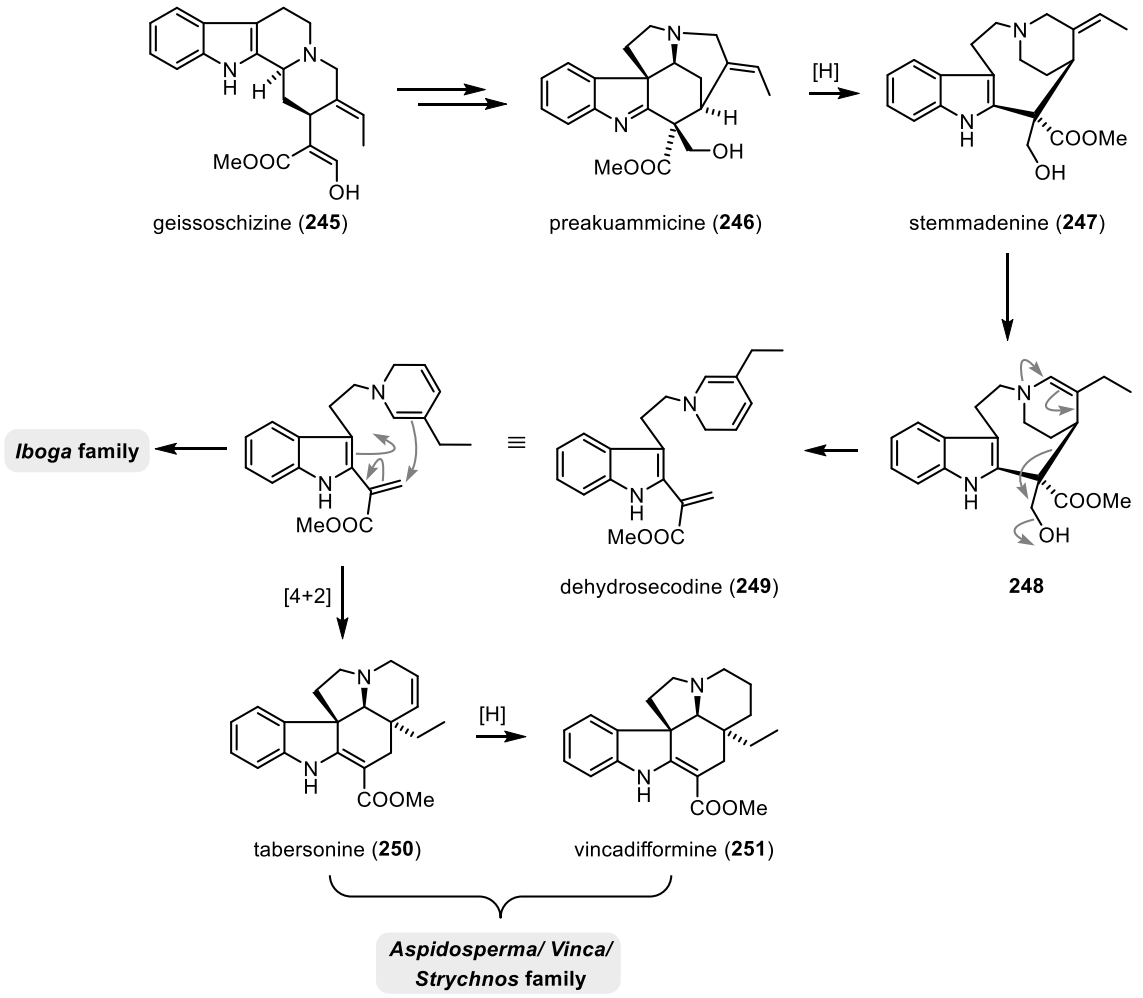
between secologanin (**239**) and tryptamine (**241**) leads to strictosidine (**242**) (Scheme 68). The *Cinchona* alkaloids are directly derived from this intermediate. Next, strictosidine (**242**) is deglycosylated to give a reactive hemi-acetal,[121] which opens to form dialdehyde **243**. This intermediate reacts with the secondary amine to form iminium ion **244**, which can either directly lead to the *Yohimbinoid* alkaloid family or to geissoschizine (**245**) after reduction. The *Ajmalicine* alkaloids are in turn derived from geissoschizine (**245**).



Scheme 68. Biosynthetic pathway to geissoschizine (**245**).

The entrance into the *Vinca*, *Aspidosperma* and *Strychnos* alkaloids starting from geissoschizine (**245**) is less understood (Scheme 69). The exact mechanism of the formation of preakuammicine (**246**) from geissoschizine (**245**) has not been fully elucidated to date. An isomerization of the exocyclic double bond to form an enamine affords intermediate **248**, which forms dehydrosecodine (**249**) after a ring-opening reaction through enzymatic dehydroxylation.

The *Iboga* alkaloids are biosynthetically derived from dehydrosecodine (**249**). A Diels−Alder reaction is then believed to result in the formation of tabersonine (**250**) and a final reduction step should lead to vincadifformine (**251**), an archetypical member and precursor for various members of the *Vinca*, *Aspidosperma* and *Strychnos* alkaloids.



Scheme 69. Biosynthetic pathway from geissoschizine (**245**) to tabersonine (**250**) and vincadifformine (**251**).

5.3 Jerantinines A−G

The monoterpene indole alkaloids jerantinine A−G (**252**−**258**) were isolated from leaf extracts of the Malayan plant *Tabernaemontana corymbose* of the *Apocynaceae* family in 2008 (Figure 7a).[122] These secondary metabolites belong to the *Aspidosperma* alkaloid subclass, which all have a characteristic pentacyclic [6.5.6.6.5]-ring system with an indole substructure in common. All compounds were isolated by extraction of the ground leaf material with ethanol and dilute acid, followed by separation of the individual compounds by column chromatography on silica gel using dichloromethane and varying amounts of methanol. Jerantinine A (**252**) constitutes the major compound isolated from the leaf extract.

a)

b)

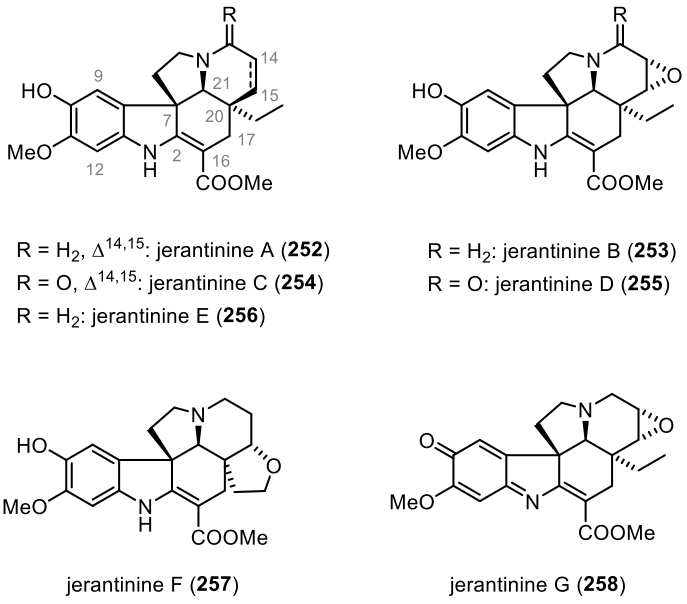
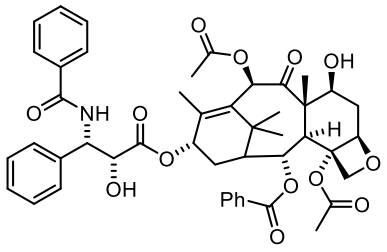


Figure 7. a) *Tabernaemontana corymbose*[§§] and b) jerantinines A−G (**252−258**).

Preliminary studies on the cytotoxicity of these alkaloids revealed in vitro cytotoxicity against human KB cells (IC_{50} = 0.28−5.1 μM) with jerantinine D (**255**) being the most potent compound (IC_{50} = 0.28 μM).[122] It was furthermore discovered that acetylation of jerantinine A (**252**) and B (**253**) resulted in an enhancement of the cytotoxic effect. Given these promising cytotoxic activities of the jerantinines, further biological studies have been directed toward a better understanding of these effects. Jerantinine A (**252**), B (**253**) and E (**256**) were later described as microtubule disrupting agents (MDA) which act by inhibition of tubulin polymerization and by inducing G_2/M cell cycle arrest.[123–126] Natural product MDAs find use in chemotherapy because cancer cells grow more quickly than normal cells through continuous mitotic division. Thus, these

[§§] photograph by BernhardM, distributed under a CC-BY-SA 2.5 license.

cells are sensitive to inhibition of mitosis. MDAs prevent cells from undergoing mitosis by disrupting microtubule polymerization by interfering with either the assembly or the disassembly of microtubule polymers.[127] One commonly used and effective MDA for the treatment of several types of cancer (e.g. breast cancer) is paclitaxel (**259**) (brand name: taxol). Paclitaxel acts by stabilizing the microtubule polymer and thus protects it from disassembly.



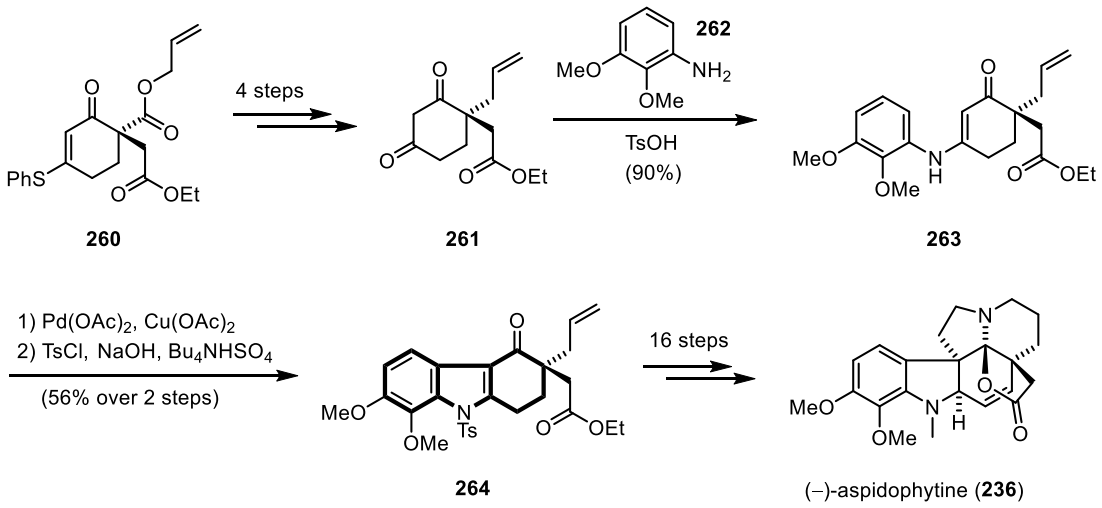
paclitaxel
(**259**)

Figure 8. The MDA paclitaxel (**259**) (brand name: taxol).

5.4 Selected Examples of Synthetic Strategies Toward *Aspidosperma* Alkaloids

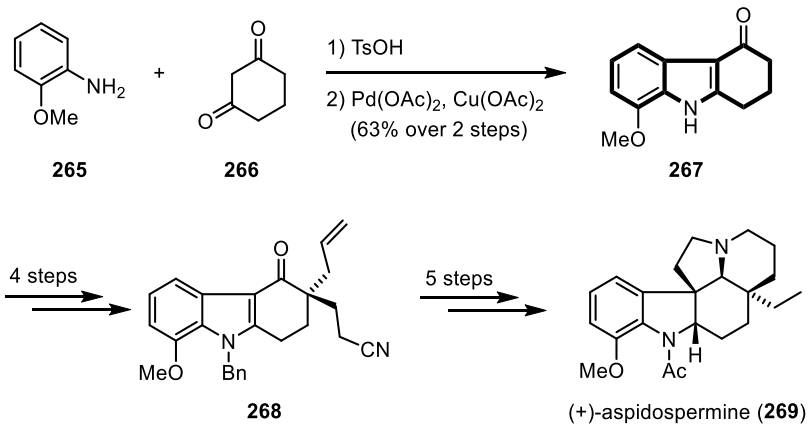
Due to their structural complexity and their remarkable biological activities, monoterpene indole alkaloids have been attractive targets for synthetic chemists for several decades. Many of these unique secondary metabolites have been synthesized in the past and several different synthetic approaches have been described in the literature.[115] Given the numerous synthetic strategies, this paragraph only highlights some recent syntheses of *Aspidosperma* alkaloids with a focus on the construction of the tricyclic tetrahydrocarbazolone core (highlighted with bold bonds).

In the first two examples, the construction of the tetrahydrocarbazolone core was realized by employing a condensation/C−H bond activation sequence. In 2013, Qiu et al. reported an asymmetric total synthesis of (−)-aspidophytine (**236**) from chiral 1,3-diketone **261** and 2,3-dimethoxyaniline (**262**).[128] Enantiopure 1,3-diketone **261** was in turn prepared from known phenylthioether **260** in four steps. The tricyclic tetrahydrocarbazolone core was constructed by a condensation reaction of 1,3-diketone **261** and 2,3-dimethoxyaniline (**262**), followed by a palladium-catalyzed oxidative indole formation. Further 16 steps then completed the total synthesis of (−)-aspidophytine (**236**) (Scheme 70).



Scheme 70. Qiu's total synthesis of (−)-aspidophytine (**236**).

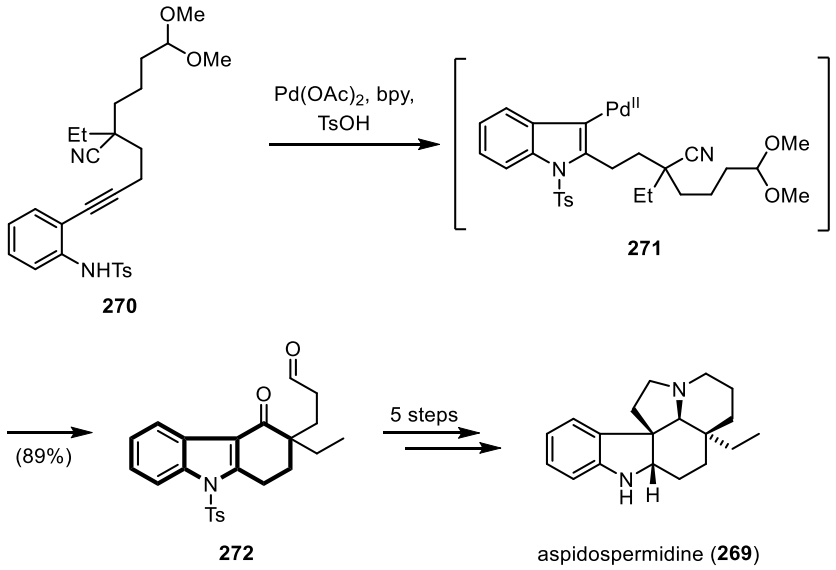
A similar synthetic strategy was employed by Shao et al. in 2014 for the asymmetric total syntheses of four different *Aspidosperma* alkaloids, including aspidospermine (**269**).[129] In his work, the tetrahydrocarbazolone core fragment **267** was prepared from 1,3-cyclohexadione (**266**) and 2-methoxyaniline (**265**) by TsOH-mediated condensation and subsequent oxidative indole formation (Scheme 71). In contrast to Qiu's work, this tricyclic intermediate was functionalized after its formation in further four steps to give tricycle **268**. The synthesis of the natural product was then finalized in five steps.



Scheme 71. Shao's total synthesis of (+)-aspidospermine (**269**).

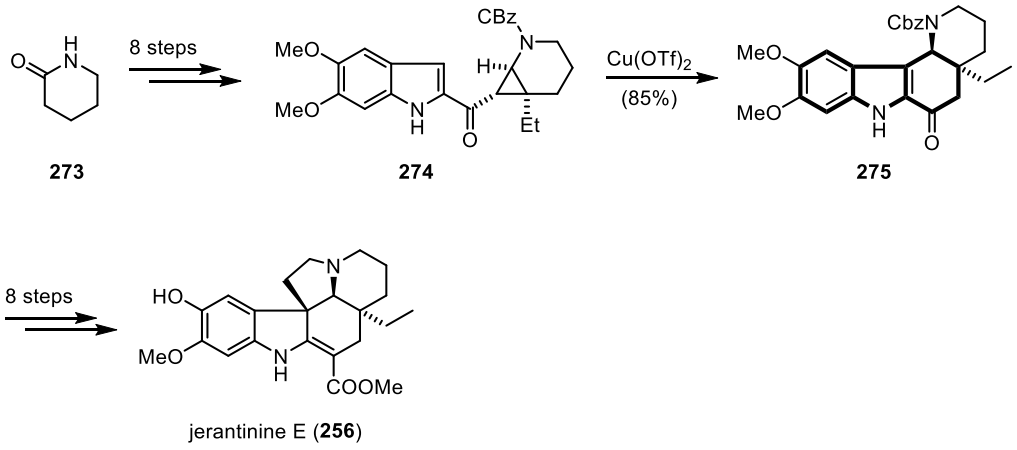
In another approach for the formal synthesis of racemic aspidospermidine (**269**), an efficient palladium(II)-catalyzed tandem reaction was employed for the synthesis of the tricyclic tetrahydrocarbazolone core of the *Aspidosperma* alkaloids (Scheme 72).[130] First, the indole core was generated by an intramolecular aminopalladation of the alkyne moiety. Second, the Pd(II)-indole intermediate **271** attacked the nitrile group to form the C ring. Furthermore, the addition of

para-toluenesulfonic acid (TsOH) resulted in a deprotection of the acetal moiety to afford aldehyde **272**. Further three steps then completed the formal synthesis of aspidospermidine (**269**).



Scheme 72. Palladium(II)-catalyzed tandem cyclization reaction for the synthesis of the ABC core of aspidospermidine (**269**).

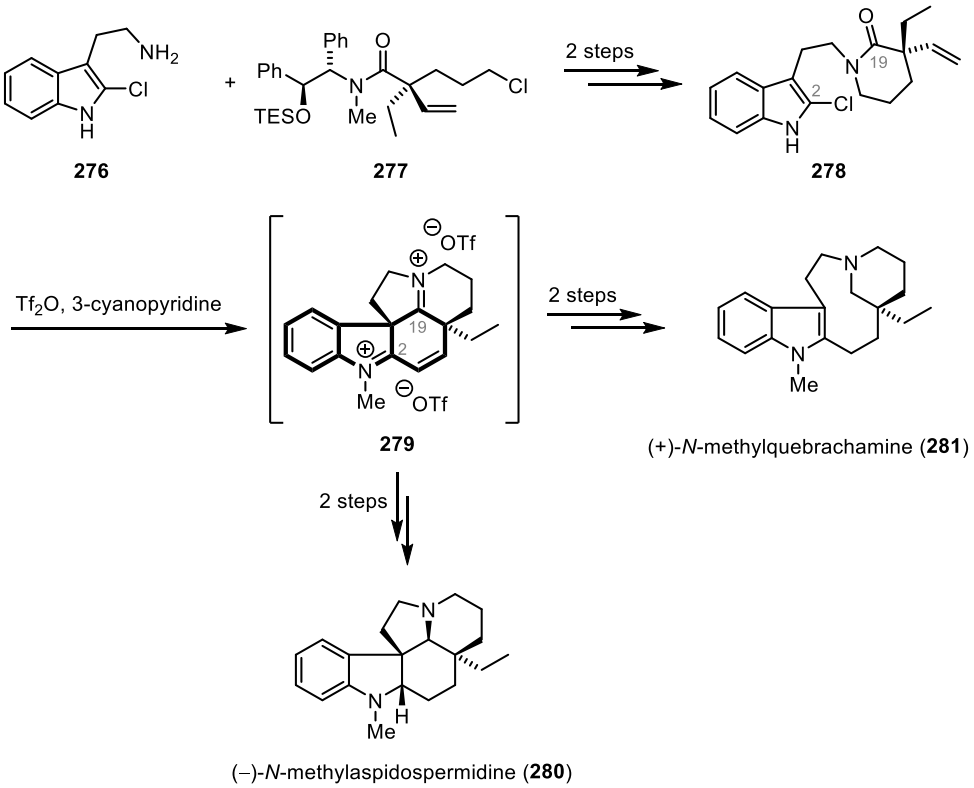
The first synthesis of a member of the jerantinines was reported by Waser in 2013 (Scheme 73).[126] For the synthesis of jerantinine E, Waser commenced with commercially available δ-valerolactone (**273**). A selective copper(II)-triflate catalyzed cyclization of aminopropane **274** (formal homo-Nazarov reaction) was employed as key reaction for the synthesis of the tetracyclic core structure of jerantinine E (**256**). The synthesis of jerantinine E (**256**) was then finalized in further eight steps.



Scheme 73. The Waser synthesis of jerantinine E (**256**).

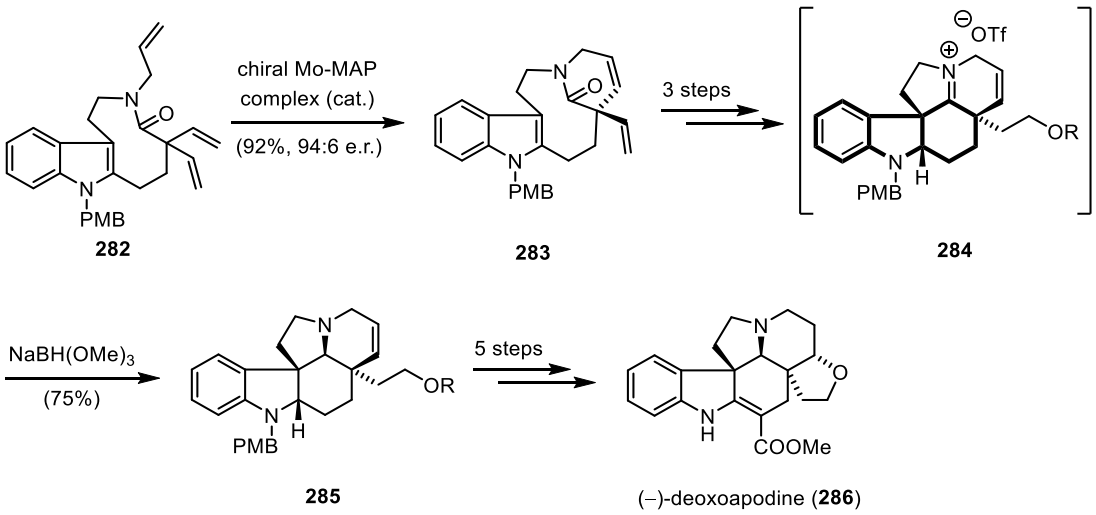
Inspired by the proposed biosynthesis of the *Aspidosperma* alkaloids (see chapter 5.2), several approaches on the utilization of indole-linked δ-lactam intermediates for the construction of the pentacyclic core structure of these natural products have been described recently. In 2012,

Movassaghi et al. reported a unique synthetic strategy for a group of structurally related *Aspidosperma* alkaloids via a double-cyclization cascade of lactam **278**.[131] The lactam **278** was prepared from C2-chlorinated tryptamine **276** and amide **277** in two steps. The remarkable key step to generate diiminium ion **279** was realized by treatment of amide **278** with trifluorosulfonic anhydride (Tf_2O) and a pyridine base. Diimimium ion **279** could then be either transformed to (+)-*N*-methylquebrachamine (**281**) or to (−)-*N*-methylaspidospermidine (**280**) in further two steps, respectively (Scheme 74).



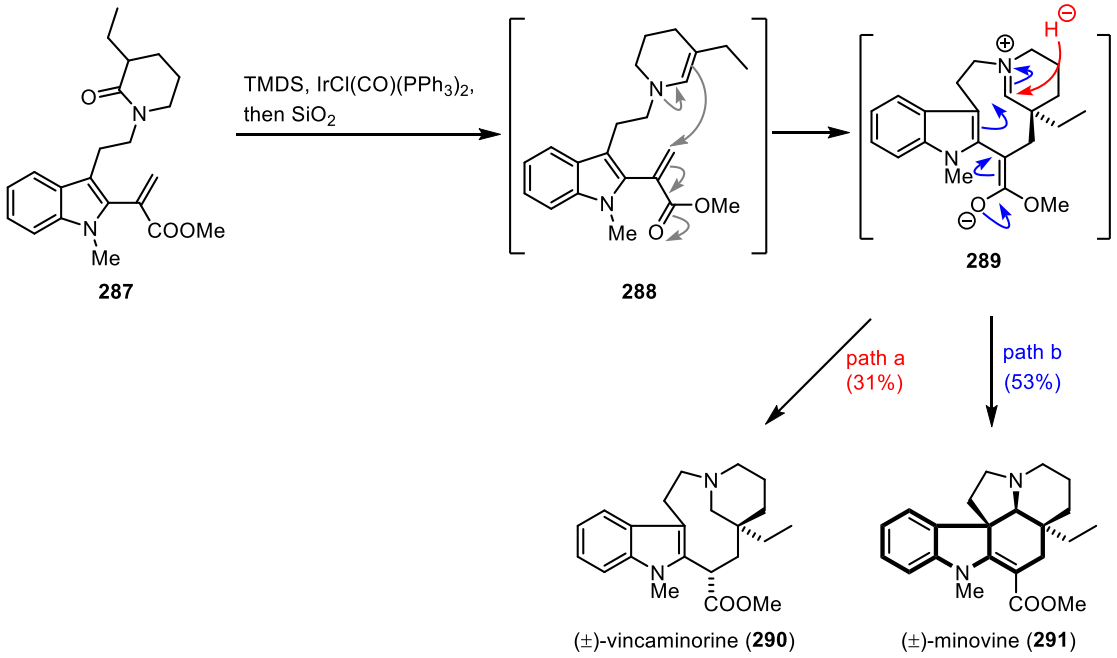
Scheme 74. Movassaghi's synthesis of different *Aspidosperma* alkaloids.

Movassaghi and Hoveyda later employed a similar synthetic strategy for the total synthesis of the *Aspidosperma* alkaloid (−)-deoxoapodine (**286**).[132] For the preparation of the key step precursor, an enantioselective ring-closing metathesis reaction was employed to afford amide **283** (Scheme 75). Amide activation with tributyltin hydride (*n*-Bu_3SnH) and Tf_2O then afforded iminium ion **284**, which could be *in situ* reduced with sodium borohydride to give the characteristic pentacyclic core structure of the *Aspidosperma* alkaloids. Further five steps, including a transannular spirocyclization, finalized the total synthesis of (−)-deoxoapodine (**286**).



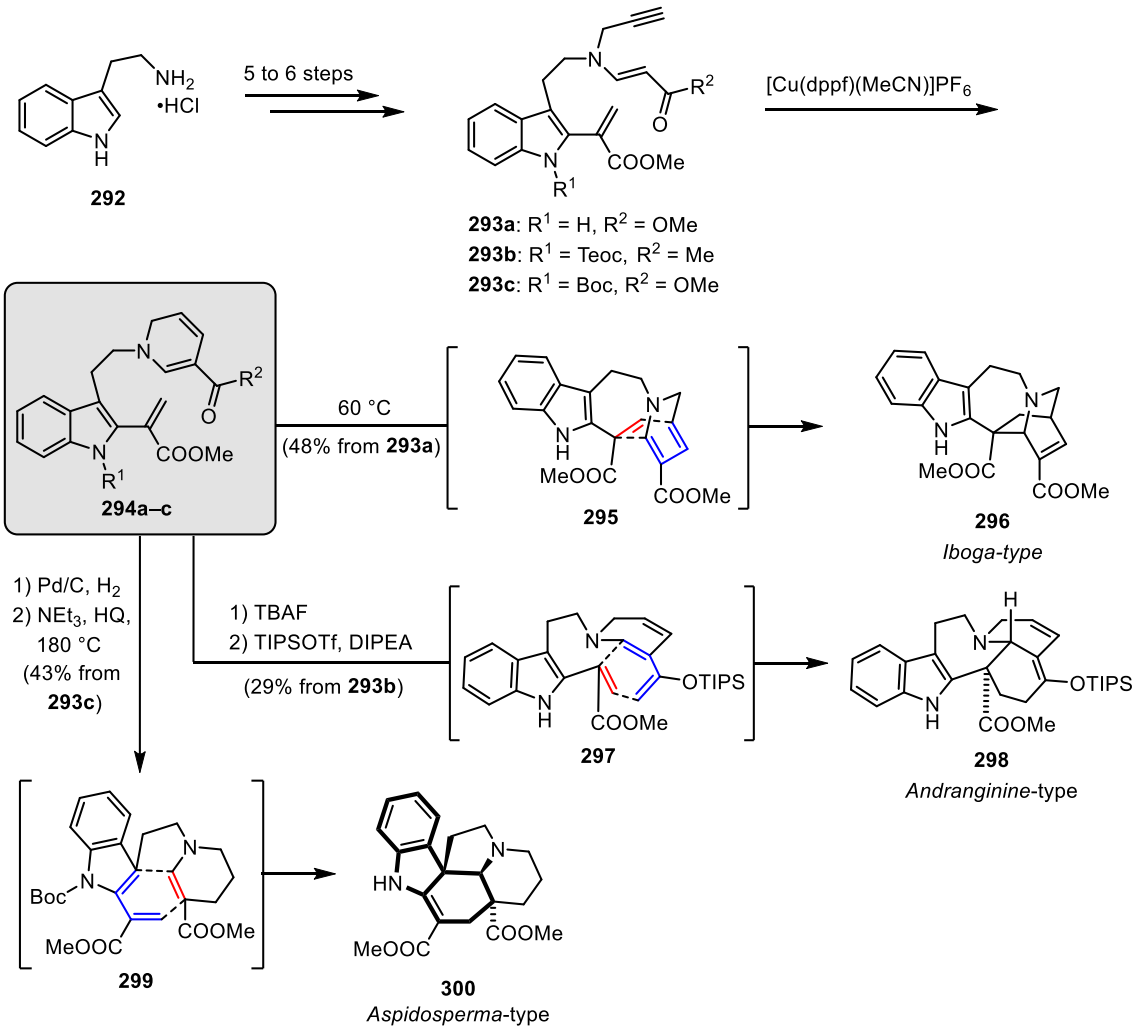
Scheme 75. Movassaghi's and Hoveyda's asymmetric total synthesis of (−)-deoxoapodine (**286**) (R = *para*-nitrobenzoyl).

In 2016, Dixon et al. reported the development of a unique cascade reaction for the synthesis of a group of *Aspidosperma* alkaloids.[133] Their key step precursor was an indole-linked δ-lactam (**287**), which was reduced to reactive enamine **288** in the presence of tetramethyldisiloxane (TMDS) under iridium(I)-catalysis (Scheme 76). This enamine then underwent an enamine Michael addition to afford betaine **289**. In two competing pathways, betaine **289** was either converted to (±)-vincaminorine (**290**) by reduction of the iminium ion (path a) or to (±)-minovine (**291**) via a transannular Mannich reaction (path b). Later, three other Aspidosperma-type alkaloids have also been synthesized by using this method.[133]



Scheme 76. Dixon's unique cascade reaction for the total synthesis of (±)-vincaminorine (**291**) and (±)-minovine (**290**).

In another biomimetic approach, Oguri et al. prepared artificial intermediates **294a–c** for the syntheses of five skeletally different indole alkaloid scaffolds (Scheme 77).[134] Their synthetic strategy was based on the imitation of the common biosynthetic intermediate dehydrosecodine (**249**), which was further converted to different types of monoterpene indole alkaloids via distinct [4+2] cycloadditions (see chapter 5.2). Starting from tryptamine hydrochloride (**292**), three different ene-ynes **293a–c** were prepared in five to six steps. Copper(I)-catalyzed cyclization of **293a**, followed by a one-pot Diels–Alder reaction afforded the skeletal scaffold of the *Iboga*-type alkaloids **296**. The *Andranginine*-type alkaloids could also be accessed from **294b** by formation of silyl enol ether **297** and by subsequent [4+2] cyclization. Furthermore, regioselective hydrogenation of **294c**, followed by another Diels–Alder reaction gave the *Aspidosperma*-type scaffold.

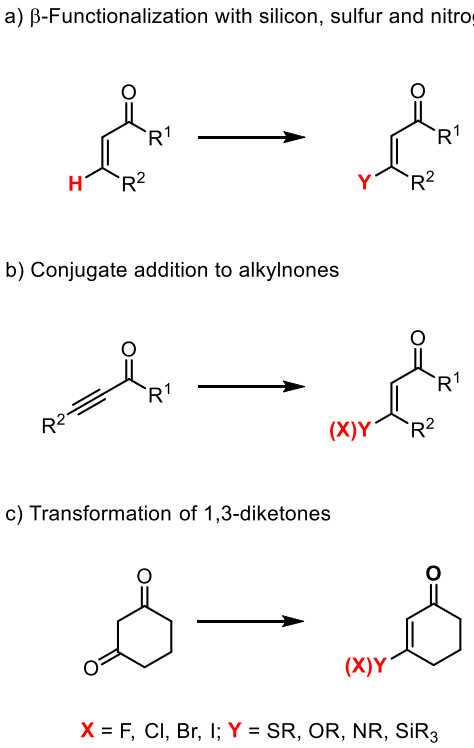


Scheme 77. Oguri's biosynthetically inspired syntheses of three different indole alkaloid scaffolds.

In summary, a large variety of methods have been developed to prepare the *Aspidosperma* skeleton over the past decades. In general, recent efforts toward the synthesis of *Aspidosperma* alkaloids have proceeded to the development of more general synthetic routes for the preparation of a group of structurally related indole alkaloids.

5.5 *β*-Halogenated Enones as Versatile Building Blocks[***]

β-Functionalized enones have found widespread application as important building blocks in organic synthesis and the corresponding *β*-acylvinyl anions and cations are important synthons for retrosynthetic planning. These compounds have been synthetically accessed by either functionalization of enones (Scheme 78a), by conjugate addition of alkynones (b) or by transformation of 1,3-diketones (c).



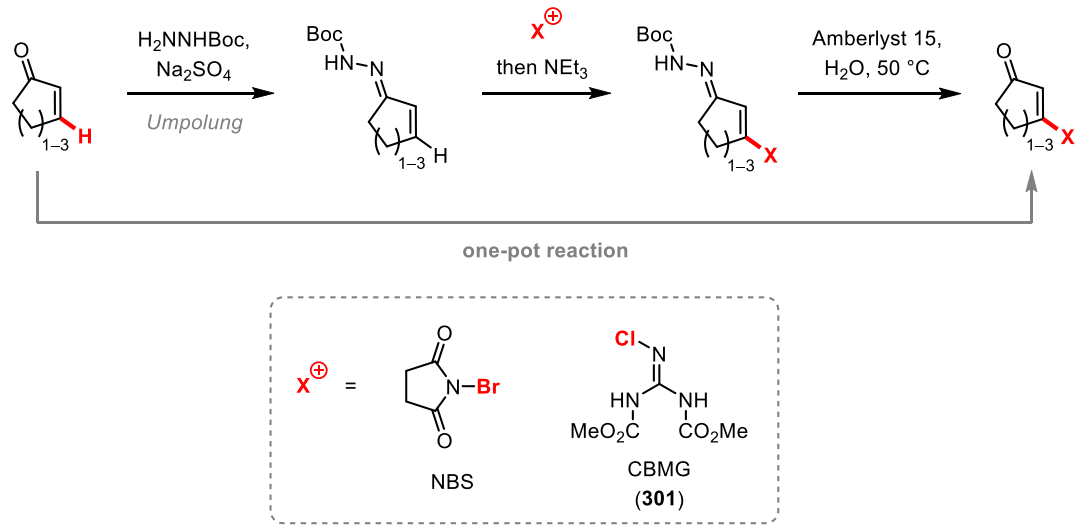
Scheme 78. Strategies for the synthesis of *β*-functionalized enones.

In recent years, the direct *β*-functionalization of enones has only been achieved with heteroatoms such as silicon,[135] sulfur[136–138] and nitrogen,[139] but not with halogens. The preparation of *β*-functionalized enones by 1,4-addition to alkynones was limited to acyclic systems and resulted in the generation of double bond isomers. For example, *β*-trimethylsilyl enones have been prepared by conjugate addition of trimethylsilyl halides to alkynones.[140–146] Additionally, (*Z*)-configured *β*-chloroenones have been accessed by Lewis acid catalyzed acylation of alkynes with gallium(III) chloride,[147] iron(III) chloride,[148] or aluminum(III) chloride.[149] The formation of *β*-functionalized enones from six-membered 1,3-diketones is a commonly employed standard transformation,

[***] This chapter has been adapted from the article *"Experimental Studies on the Selective β-C–H Halogenation of Enones"* – T. Huber, D. Kaiser, J. Rickmeier, T. Magauer, *J. Org. Chem.* **2015**, *80*, 2281−2294.

especially for the synthesis of *β*-halogenated enones.[150–153] The reaction usually proceeds with high regioselectivity if the six-membered 1,3-diketone is substituted symmetrically. The halogenation of unsymmetrical substituted 1,3-diketones was found to be unselective and resulted in the formation of product mixtures.[150]

The commercial availability and the ease of preparation of many *α,β*-unsaturated carbonyl compounds made the development of a direct procedure for the *β*-C−H halogenation an attractive research field. Thus, a novel method for the *β*-selective bromination and chlorination of five- to seven-membered cyclic enones has been developed in the Magauer research laboratories during my Master thesis.[154] Our developed one-pot three step protocol was based on fundamental work by Severin.[155,156] In his work, the general strategy was the Umpolung of the electrophilic β-position of the carbonyl group through hydrazone formation. The *α,β*-unsaturated hydrazones could be regioselectively halogenated using bromine, chlorine or iodine. Unfortunately, the procedure suffered from harsh reaction conditions for the introduction and the cleavage of the hydrazones, as well as from incompatibility of the individual steps. We therefore set out to develop a conceptual similar methodology that should convert enones to *β*-halo enones in one flask. Hydrazone formation was best achieved by heating a mixture of the enone and *tert*-butyl carbazate ($BocNHNH_2$) in 1,2-dichloroethane in the presence of sodium sulfate as drying agent (Scheme 79). The following halogenation was then efficiently mediated by *N*-bromosuccinimide (NBS), or by Palau'chlor (**301**, CBMG = 2-chloro-1,3-bis(methoxycarbonyl)guanidine) in dichloromethane.[157] Hydrolysis of the hydrazone moiety was achieved by heating the reaction mixture to 50 °C in the presence of Amberlyst 15, an acidic ion exchange resin.



Scheme 79. The one-pot procedure for the *β*-C−H halogenation of enones by the Magauer group.

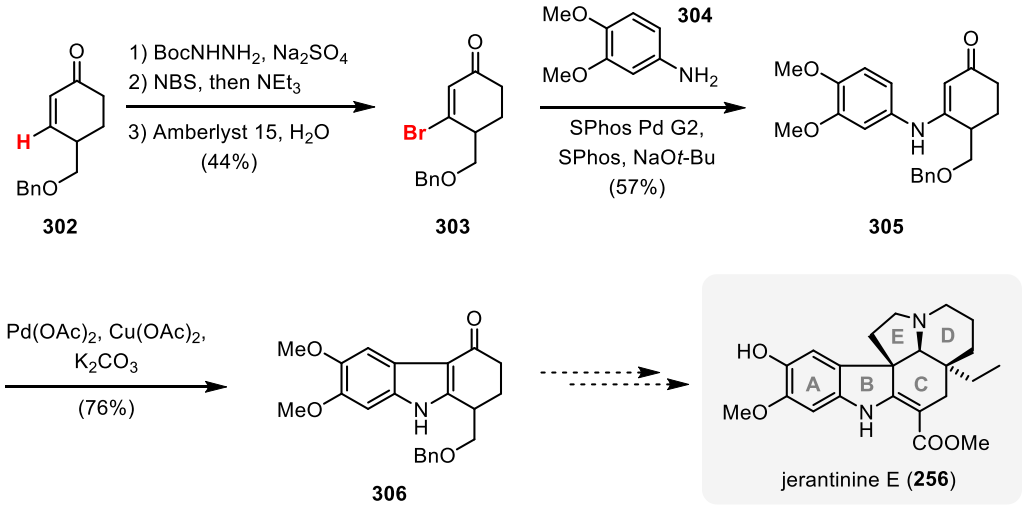
These relatively mild conditions allowed us to perform the three individual steps in one flask. With the optimized one-pot procedure in hand, cyclic enones with different substitution patterns could

be successfully brominated or chlorinated in their β-position. Various functional groups, including alkynes, nitriles, esters, alcohols and ethers, were tolerated under these conditions.

6 Project Outline

6.1 Previous Work

In earlier studies during my Master thesis, a short and modular synthesis of the tricyclic core structure of the *Aspidosperma* alkaloid jerantinine E (**256**) has been developed to further demonstrate the utilization of our newly established one-pot procedure for the selective *β*-halogenation of enones (Scheme 80).[154] Racemic enone **302** was readily prepared by alkylation of *β*-ethoxy cyclohex-2-en-1-one with benzyl chloromethyl ether (BOMCl) and subsequent Stork−Danheiser enone transposition.[158] The following one-pot *β*-C−H bromination was performed in good yield over three steps (44%) on a 5 mmol scale to give *β*-bromo enone **303**. The aromatic amine fragment was then installed via palladium-catalyzed amination of *β*-bromo enone **303** with 3,4-dimethoxyaniline (**304**). Palladium-catalyzed oxidative indole formation of enaminone **305** finally afforded the tricyclic ABC core structure **306** of jerantinine E (**256**). In conclusion, this three-step sequence allowed for the efficient and modular preparation of tetrahydrocarbazolone structures.



Scheme 80. Synthesis of the tricyclic jerantinine E core **306**.

6.2 Aims and Significance of the Project

It was the second goal of this Ph.D. thesis to continue our studies directed toward the total synthesis of jerantinine E (**256**). All retrosynthetic considerations should be based on the use of a substituted *β*-bromo enone as building block, which should be prepared by our one-pot *β*-C−H bromination protocol. While the reported three-step sequence for the construction of the tricyclic core structure of jerantinine E (**256**) has only been carried out in a racemic fashion, future studies should also be directed to the realization of an asymmetric synthesis. Compared to other reported synthetic routes for the construction of the tetrahydrocarbazolone core structure of *Aspidosperma* alkaloids, our

synthetic approach allows structural modifications prior to assembly of the tetrahydrocarbazolone fragment. This is especially useful for the synthesis of indole alkaloids with a highly oxygenated indole core (A/B rings) and/or a highly substituted C ring. Furthermore, the installation of the D and E ring of the natural product should be examined.

7 Results and Discussion

7.1 Development of a *β*-C–H Bromination Approach Toward the Synthesis of Jerantinine E

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Development of a β-C−H Bromination Approach toward the Synthesis of Jerantinine E

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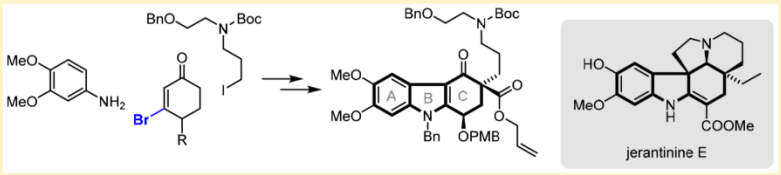
Supporting Information



ABSTRACT: The development of an asymmetric and highly convergent three-component synthesis of the functionalized ABC ring system of the *Aspidosperma* alkaloid jerantinine E is reported. The presented synthetic strategy relies on our recently developed method for the one-pot β-C−H bromination of enones, which allows for rapid construction of the tricyclic tetrahydrocarbazolone core via a palladium-catalyzed amination and oxidative indole formation. Moreover, a secondary amine building block that contains all carbon atoms of the D and E ring of the natural product could be installed in three additional steps.

■ INTRODUCTION

Monoterpenoid indole alkaloids have been attractive targets for synthetic chemists for several decades, and many of their unique skeletons have been synthesized in the past.[1] In addition to their daunting structural complexity, a variety of biological activities and medicinal applications have been reported, including anticancer (e.g., jerantinine E, vinblastine, brucine)[2] and insecticidal (e.g., aspidophytine)[3] activities (Figure 1A). The *Aspidosperma* alkaloid subfamily consists of more than 250 different members and biosynthetically originates from the condensation of tryptamine with a rearranged secologanin-derived C_9 or C_{10} terpene unit.[4] The secondary metabolites jerantinine A−G (Figure 1B) were isolated in 2008 from leaf extracts of the Malayan plant *Tabernaemontana corymbosa* and exhibit cytotoxic effects against vincristine-sensitive and vincristine-resistant epidermoid carcinoma cell lines (IC_{50} = 0.68−2.55 μM).[2a] In 2013, Waser reported the first synthesis of the *Aspidosperma* alkaloid jerantinine E (**1**) in 17 steps[5] and disclosed its antiproliferative activity against several human-derived breast and lung cancer cell lines (IC_{50} = 1.0−6.0 μM) mediated by inhibition of tubulin polymerization.

In the course of our studies toward novel methods for the site-selective functionalization of α,β-unsaturated compounds,[6] we identified several monoterpenoid indole alkaloids that could be retrosynthetically traced back to a β-halogenated enone. Despite significant advances made in the functionalization of α,β-unsaturated compounds in recent years,[7] only two examples for the direct β-halogenation of enones are known.[8] The syntheses of *Aspidosperma* alkaloids by Desmaële[9] and Qiu[10] both require multistep sequences relying on prefunctionalized vinylogous thioesters for the preparation of the crucial β-enaminone subunit common to several *Aspidosperma* alkaloids (Scheme 1A). We could circumvent these rather inefficient transformations by our two-step sequence starting from simple enones (Scheme 1B). Herein, we describe a convergent synthesis of the ABC ring system of the oxygenated indole alkaloid jerantinine E (**1**) employing our recently developed protocol for the one-pot β-C−H bromination of enones.[6]

■ RESULTS AND DISCUSSION

Our retrosynthetic analysis of **1** was guided by the proposed use of β-bromo enone **11** (Figure 1B) as a general entry to polycyclic indole alkaloids. Identification of this subunit in jerantinine E (**1**) inspired the strategy illustrated in Scheme 2A. In our analysis, tetracycle **12** would arise from the sequential diastereoselective alkylation of the tetrahydrocarbazolone **13** with iodide **14** and ethyl iodide. For the construction of the D-ring of **1**, we envisioned a sequence that would be initiated by the reduction of the ketone and subsequent acid-mediated elimination of the alcohol followed by in situ addition of the free amine to the resultant vinylogous iminium ion **19** (Scheme 2B).[11] The tetrahydrocarbazolone **13** was traced back to 3,4-dimethoxyaniline (**15**) and β-bromo enone **16** which in turn could be accessed via β-C−H bromination of the parent enone.

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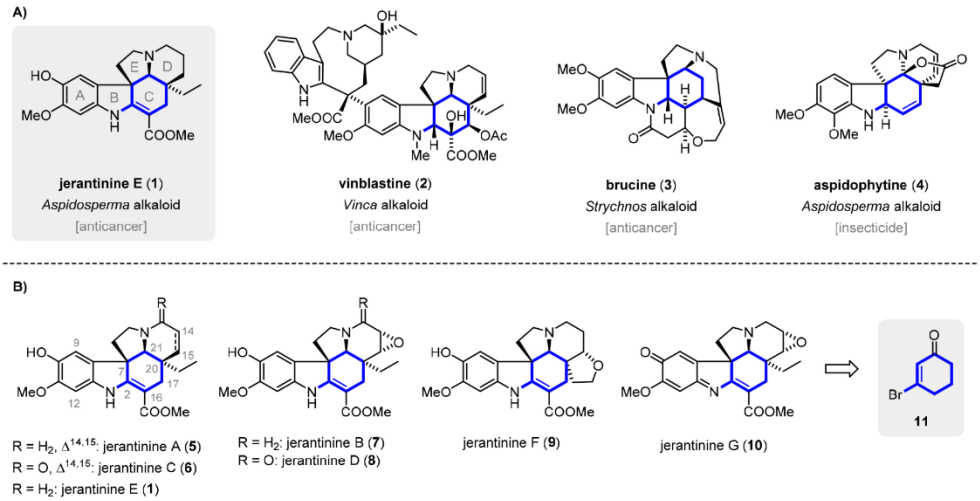
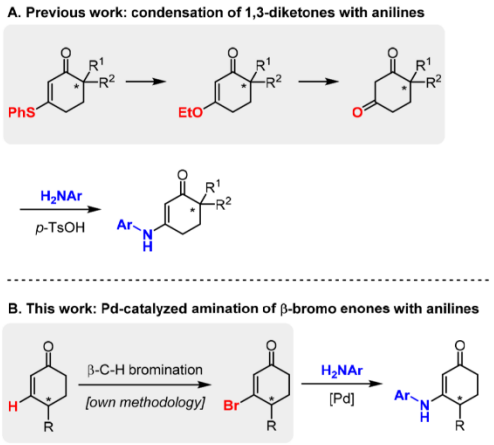


Figure 1. (A) Naturally occurring indole alkaloids and (B) structures of jerantinines A–G.

Scheme 1. Methods for the Preparation of Functionalized *β*-Enaminones for the Synthesis of *Aspidosperma* Alkaloids



In an initial attempt to synthesize jerantinine E (**1**), we targeted racemic intermediate **12**. The synthesis started with our previously reported preparation of tetrahydrocarbazolone *rac*-**13**, prepared in three steps from enone **21** utilizing a *β*-C–H bromination, a palladium-catalyzed amination with 3,4-dimethoxyaniline (**15**), and oxidative indole formation (Scheme 3).[6] Finally, tetrahydrocarbazolone *rac*-**13** was Boc-protected to give **22** in a good yield (88%). To examine the introduction of secondary amine **14**, we performed first alkylation with 1-chloro-3-iodopropane as a model electrophile. Treatment of **22** with lithium bis(trimethylsilyl)amide (LHMDS) and an excess of 1-chloro-3-iodopropane followed by nucleophilic displacement of the chloride provided azide **23**. Unfortunately, alkylation of **23** by treatment with LHMDS and ethyl iodide did not give the desired product. Instead, the elimination of the benzyl ether to give alkene **24** was observed,[12] which was prone to aromatization upon exposure to traces of acid.

Since **23** underwent undesired elimination under basic alkylation conditions, we contemplated exchange of the CH_2OBn moiety for a protected hydroxy group in the *γ*-position of the enone. Our revised retrosynthetic analysis featured the synthesis of a modified, asymmetric tetrahydrocarbazolone core structure which could be constructed from 3,4-dimethoxyaniline (**15**), secondary amine building block **14**, and enantiopure *β*-bromo enone **27** (Scheme 4). The stereocenter of the latter component was planned to direct the sequential introduction of the side chains and enable the asymmetric total synthesis of jerantinine E (**1**).

We began our endeavor with the synthesis of known chiral alcohol **29**, itself derived from 1,4-cyclohexanedione monoethylene acetal (**28**) in four steps.[13] Protection of **29** as its *para*-methoxybenzyl ether (PMB) using Dudley's reagent II (2-(4-methoxybenzyloxy)-4-methylquinoline)[14] furnished **30**. Enone **30** was then subjected to our conditions for one-pot *β*-C–H bromination, which includes (1) umpolung of the enone by hydrazone formation with *tert*-butyl carbazate (*tert*-butoxycarbonyl hydrazide), (2) selective *β*-C–H bromination with *N*-bromosuccinimide (NBS) followed by addition of triethylamine to isomerize the allyl bromide, and (3) hydrolysis of the hydrazone moiety, to afford **27** in 57% yield on a 340 mg scale (Scheme 5). Palladium-catalyzed amination with 3,4-dimethoxyaniline (**15**) employing Buchwald's SPhos second generation precatalyst[15] followed by an oxidative indole formation[16] using palladium acetate and copper acetate furnished **32**. It is noteworthy that careful monitoring of the C–H activation reaction proved to be crucial to avoid overoxidation and subsequent hydrolysis of the PMB ether with extended reaction times. Benzyl protection of the tetrahydrocarbazolone **32** provided **33**,[17] whose structure could be validated by single-crystal X-ray diffraction.[18]

Having developed a short and efficient synthesis of key intermediate **33**, the stage was set for the installation of the quaternary stereocenter as the crucial handle to construct the DE ring system of jerantinine E (**1**). However, in sharp contrast to the results obtained for the alkylation of **22**, direct alkylation of **33** with ethyl iodide was not feasible under a variety of conditions. The use of LHMDS, LDA, or LDA/HMPA only led

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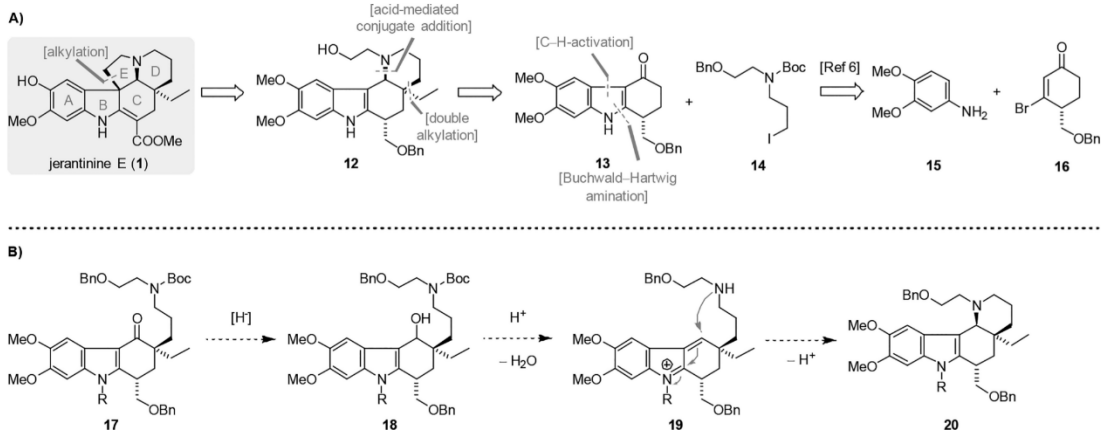
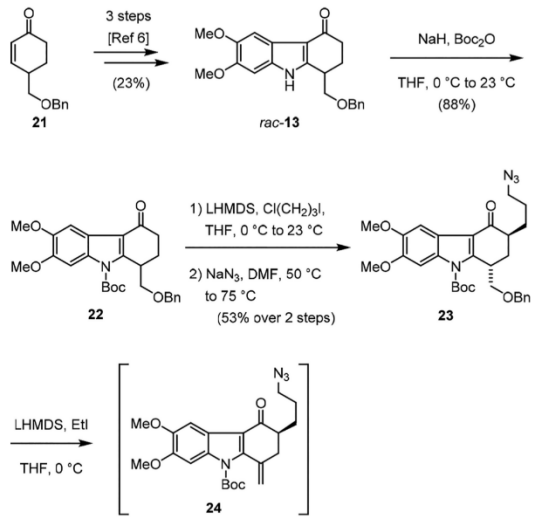
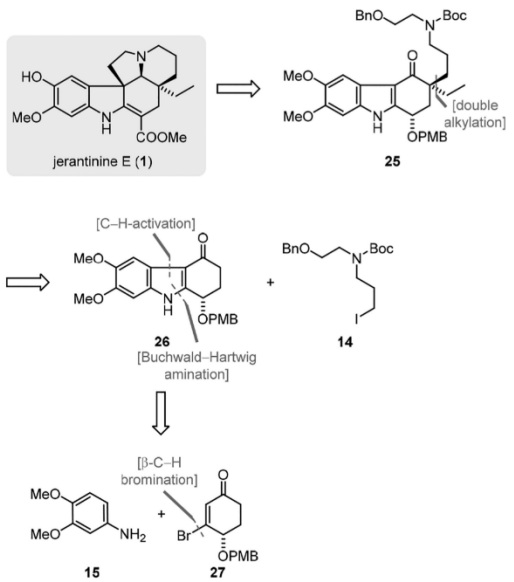
Scheme 2. (A) Initial Retrosynthetic Analysis of Jerantinine E (1) and (B) Envisioned Cascade Reaction for the Construction of the D-Ring



Scheme 3. Synthesis of Tetrahydrocarbazolone 22 and Alkylation with a Model Electrophile



Scheme 4. Revised Retrosynthetic Analysis of Jerantinine E (1)



to recovered starting material. The exact influence of the substituent at the γ-position of the ketone and the protecting groups (Bn and PMB) on the alkylation is unclear.

To overcome this poor reactivity, we investigated the acylation of **33**. Surprisingly, exposure of **33** to LHMDS and Mander's reagent[19] (methyl cyanoformate) at −78 °C followed by alkylation with sodium hydride and ethyl iodide proceeded cleanly and furnished **34** in good yields (Scheme 6). Next, we attempted to convert **34** to **35** by means of a decarboxylation using lithium chloride in aqueous dimethylformamide and subsequent reaction using acrylonitrile as a reactive model electrophile. Although traces of the decarboxylated product were observed, we were unable to detect any of the conjugate addition product.

Based on the successful alkylation of the β-keto ester with ethyl iodide, we decided to investigate the alkylation of **33** using iodide **14**. Thus, the Boc-protected amine building block **14** was synthesized as illustrated in Scheme 7A. Alkylation of commercially available *tert*-butyl *N*-allylcarbamate (**36**) with literature known iodide **37** under standard conditions (NaH, DMF) afforded **38** in good yield (80%).[20] Hydroboration of **38** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup using aqueous hydrogen peroxide furnished alcohol **39**. The latter was then transformed into iodide **14**, employing Appel's conditions (I_2, PPh_3, imH). With iodide **14** and tricyclic key intermediate **33** in hand, we were poised to examine the challenging fragment coupling. Acylation of **33** followed by reaction of the β-keto ester with sodium hydride and iodide **14** furnished the quaternary stereocenter in **40** in good yield (Scheme 7B). Thus, the introduction of the secondary amine building block could be accomplished in an efficient manner. The methyl ester of **40** could then be

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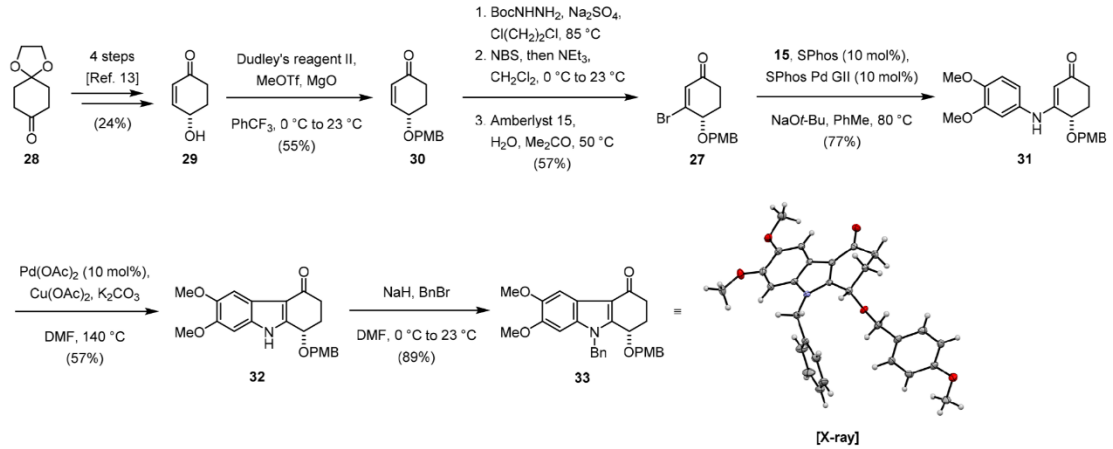
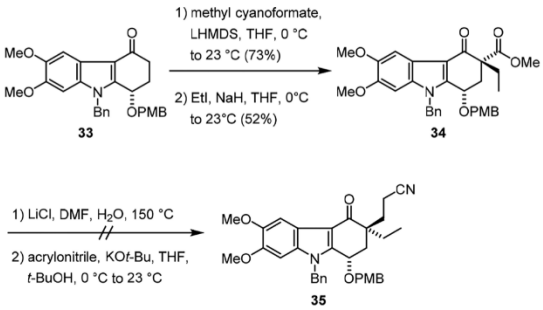
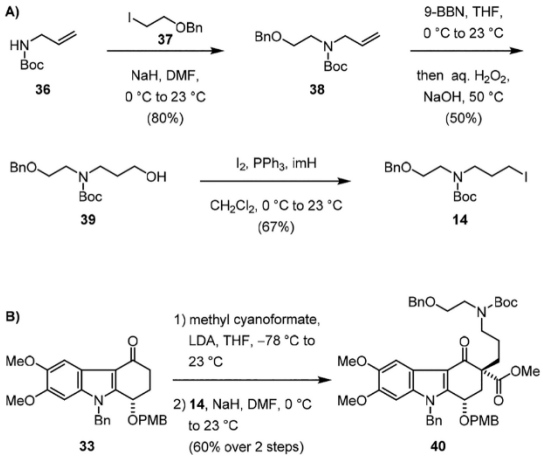
Scheme 5. Synthesis of Tetrahydrocarbazolone 33



Scheme 6. Attempted Formation of the Quaternary Stereocenter



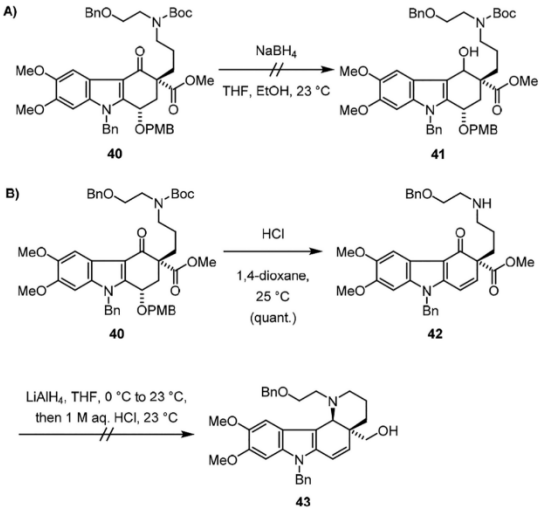
Scheme 7. (A) Preparation of the Boc-Protected Amine Building Block 14 and (B) Introduction of the Quaternary Stereocenter



transformed to the ethyl group of the natural product at a later stage of the synthesis.

For the construction of the D-ring of **1** (see Scheme 1B), we first tried to selectively reduce **40** using sodium borohydride (Scheme 8A). Since these conditions turned out to be

Scheme 8. Attempted Closure of the D-Ring of Jerantinine E



ineffective and no conversion was observed, we opted for more forcing conditions. As direct reduction of **40** with lithium aluminum hydride could not be considered due to concomitant reduction of the Boc protecting group, **40** was treated with 4 M hydrochloric acid in 1,4-dioxane to remove the Boc protecting group (Scheme 8B). Unfortunately under these conditions, deprotection of the Boc group and elimination of the PMB ether occurred, giving compound **42** as the major product. Exposure of the crude reaction mixture to lithium aluminum hydride followed by treatment with either 1 M aqueous hydrochloric acid or Rochelle's salt did not afford any detectable amounts of tetracycle **43**. Attempts to remove the Boc group under basic conditions (K_2CO_3, DMSO/H_2O, 65 °C; DIBAL-H, CH_2Cl_2, 23 °C) without affecting the PMB

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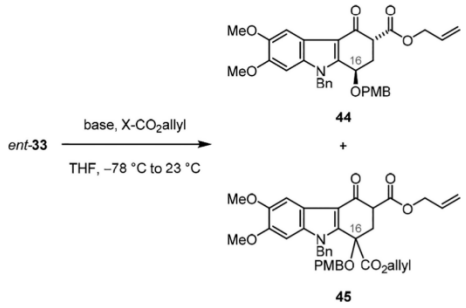
group were unsuccessful, and only complex product mixtures were obtained.

In order to avoid these undesired pathways in the functionalization of **40**, we decided to replace the methyl with an allyl ester and set the quaternary stereocenter in a subsequent diastereoselective palladium-catalyzed decarboxylative allylation reaction.[21] The obtained allyl group could then be converted to the ethyl group in three additional steps.[22] We anticipated that the stereochemical outcome of the allylation step could be controlled by the stereocenter at C16. To obtain the desired stereochemistry in the decarboxylative allylation reaction, we prepared *ent*-**33** according to the route described above.[23]

For the incorporation of the allyl ester, we examined the conditions shown in Table 1. Initially, the acylation reaction of

Table 1. Screen of Conditions for the Acylation of *ent*-33[a]



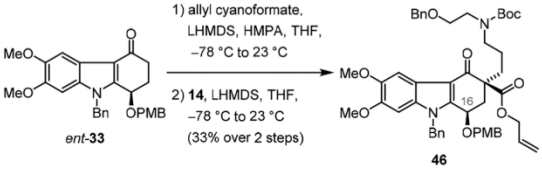
entry	base	X	product: yield[b]
1[c]	NaH	Cl	–
2	LDA	Cl	**45**: 24%
3	LHMDS	Cl	**45**[d]
4	LiTMP	Cl	**45**[d]
5	LTBTA	Cl	**45**[d]
6	LDA	im	**45**[d]
7	LHMDS	im	**45**[d]
8	LDA	CN	**44**: 42%
9	LHMDS	CN	**44**: 62%
10[e]	**LHMDS, HMPA**	**CN**	**44**: 70%

[a]All reactions were performed on a 0.02 mmol scale in THF (c = 0.02 M) with 1.1−1.2 equiv of base and 1.2 equiv of electrophile. [b]Yields of isolated products. [c]The reaction was performed at 0 °C. [d]The reactions were monitored by ^{1}H NMR spectroscopy. The yields were not determined. [e]2 equiv of HMPA were used as additive. LiTMP = lithium 2,2,6,6-tetramethylpiperidide, LTBTA = lithium *tert*-butyltrityl-amide, im = 1-imidazoyl.

ent-**33** with sodium hydride (1.1 equiv) and commercially available allyl chloroformate (1.2 equiv) at −78 °C resulted in no product formation. Surprisingly, treatment of *ent*-**33** with lithium diisopropylamide (LDA, 1.2 equiv) and allyl chloroformate (1.2 equiv) resulted in the formation of the diacylated product **45** (entry 2). Extensive screening using a variety of lithium amide bases and allyl chloroformate or allyl 1*H*-imidazole-1-carboxylate failed to provide β-keto ester **44**, and only formation of the diacylated product was observed (entries 3−7). Based on our previous findings that acylation of **44** works best with methyl cyanoformate, we investigated the use of allyl cyanoformate. This modification resulted in the formation of β-keto ester **44** for the first time (entry 8, 42%). Further optimization of the reaction conditions by variation of lithium amide bases and solvents revealed that the use of LHMDS (1.5 equiv) in the presence of hexamethylphosphoramide (HMPA, 2 equiv) is crucial to reproducibly obtain **44** in good yield (70%).

Finally, treatment of **44** with LHMDS, HMPA, and iodide **14** resulted in the smooth formation of β-keto ester **46** (Scheme 9). Other alkylation conditions explored (Cs_2CO_3, MeCN; NaH, DMF; KHMDS, THF) were inferior. Unfortunately, initial attempts to induce the palladium-catalyzed decarboxylative allylation reaction ($Pd(PPh_3)_4$ or $Pd_2(dba)_3$, (*S*)-*t*-Bu-PHOX)[24] only resulted in decarboxylation without incorporation of the allyl group. A more exhaustive screen of ligands is currently underway in our laboratories and should ultimately allow us to complete the total synthesis of jerantinine E.

Scheme 9. Successful Alkylation with Building Block 14



CONCLUSION

We have reported a synthetic route toward the total synthesis of the *Aspidosperma* alkaloid jerantinine E (**1**). The presented strategies rely on an efficient one-pot β-C−H bromination protocol to provide the C-ring subunit of the target structure. A palladium-catalyzed amination reaction was used to further functionalize the β-bromo enones and oxidative indole formation enabled formation of the tricyclic ABC tetrahydrocarbazolone fragment of jerantinine E (**1**). Our initial strategy to construct the functionalized tricyclic key intermediate of the natural product was hampered by the base-mediated elimination of the benzyl ether at C16 of the C-ring. Starting from a γ-hydroxylated enone instead, we were able to prepare highly functionalized precursor **46**. The overall sequence to the functionalized tetrahydrocarbazolone core of **1** proceeds in 11 linear steps from commercially available ketone **28** and the secondary amine component **14**. The latter contains all carbon atoms of the D and E rings of the natural product. The presented strategy is amenable to rapid modification to give a variety of tetrahydrocarbazolone structural motifs.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in oven-dried or flame-dried glassware fitted with rubber septa under a positive pressure of argon unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone and sodium prior to use. Dichloromethane (CH_2Cl_2), triethylamine (NEt_3), and *N*,*N*-diisopropylamine (DIPA) were distilled from CaH_2 prior to use. Commercially available *N*-bromosuccinimide (NBS) was purified by recrystallization from water.[25] All other reagents and solvents were purchased from commercial suppliers and were used without further purification. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC). The TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and exposure to either an aqueous solution of ceric ammoniummolybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or CD_2Cl_2. Proton chemical shifts are expressed in parts per million (δ scale) and

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are calibrated using residual undeuterated solvent as an internal reference. Additionally to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. Infrared (IR) spectra were recorded on an FT-IR spectrometer. IR data are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) or electron ionization (EI) using a sector field mass spectrometer. Melting points (Mp's) were determined on a B-450 melting point apparatus from BÜCHI Labortechnik AG. Optical rotations were recorded on a PerkinElmer 241 or Anton Paar MCP 200 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{T[^\circ C]}$ (c [g/100 mL], solvent). X-ray structural analyses were performed on a diffractometer using Mo Kα radiation (λ = 0.71073 Å, graphite monochromator).

Preparation of Azide 19. *N-Boc-tetrahydrocarbazolone* ***22***. To a solution of tetrahydrocarbazolone *rac*-**13**[6] (80 mg, 0.22 mmol, 1 equiv) in tetrahydrofuran (2.74 mL) was added sodium hydride (13 mg, 0.3 mmol, 1.5 equiv, 60% dispersion in mineral oil) at 0 °C. After 30 min, di-*tert*-butyl dicarbonate (72 mg, 0.3 mmol, 1.5 equiv) was added and the solution was allowed to warm to 23 °C. After 1.5 h, the solution was diluted with saturated aqueous ammonium chloride solution (10 mL) and diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **22** as a white solid (90 mg, 88%). TLC (25% ethyl acetate in hexane): R_f = 0.38 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.71 (s, 1H), 7.34−7.24 (m, 5H), 4.60 (d, J = 12.1 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.09−4.02 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.78 (dd, J = 9.2, 3.8 Hz, 1H), 3.62 (app t, J = 9.1 Hz, 1H), 2.72 (ddd, J = 17.4, 14.4, 5.2 Hz, 1H), 2.52−2.42 (m, 2H), 2.33−2.22 (m, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 149.7, 149.4, 147.9, 147.6, 138.1, 130.3, 128.5, 127.9, 127.9, 118.6, 117.9, 102.9, 99.3, 85.5, 73.2, 69.4, 56.3, 56.2, 34.8, 33.9, 28.2, 25.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2937, 1736, 1660, 1550, 1493, 1475, 1453, 1369, 1307, 1251, 1209, 1134 cm^{-1}. HR-MS (EI): calcd for $(C_{27}H_{31}O_6N)^+$: 465.2146; found, 465.2150.

Azide ***23***. *N*-Boc-tetrahydrocarbazolone **22** (12 mg, 0.026 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.3 mL) and 1-chloro-3-iodopropane (21.1 mg, 0.10 mmol, 4.00 equiv) was added. The solution was cooled to 0 °C, and a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 36 μL, 0.036 mmol, 1.40 equiv) was added dropwise over 6 min. After 2 h, the reaction mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with diethyl ether (5 mL), one drop of acetic acid was added, and the resulting suspension was filtered through a fritted glass funnel (Por. 4). The filter cake was rinsed with diethyl ether (10 mL). The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the chloride as a colorless oil (8.8 mg, dr = 5:1). No separation of the two diastereomers could be achieved, and the diastereomeric mixture was used for the next step.

The chloride was dissolved in *N*,*N*-dimethylformamide (0.16 mL), and sodium azide (5.3 mg, 0.08 mmol, 5.00 equiv) was added. The reaction mixture was stirred at 50 °C for 2 h, and then the temperature was increased to 75 °C. After 5 h, heating was ceased and the reaction mixture was diluted with water (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **23** as a yellow oil (7.5 mg, 53% over 2 steps, dr = 5:1). The major diastereomer could be separated by flash column chromatography. TLC (25% ethyl acetate in hexanes): R_f = 0.48 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (s, 1H), 7.37−7.25 (m, 5H), 4.63 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.09−4.04 (m, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.80 (dd, J = 9.1, 3.9 Hz, 1H), 3.63 (t, J = 9.1 Hz, 1H), 3.33 (t, J = 7.0 Hz, 2H), 2.67 (ddd, J = 17.9, 8.3, 4.7 Hz, 1H), 2.52 (ddd, J = 13.4, 4.7, 2.1 Hz, 1H), 2.11−1.99 (m, 2H), 1.76−1.70 (m, 2H), 1.67 (s, 9H), 1.48−1.43 (1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 149.7, 148.8, 147.9, 147.6, 138.0, 130.5, 128.6, 128.0, 128.0, 118.7, 117.8, 102.8, 99.4, 85.6, 73.3, 69.5, 56.3, 56.2, 51.9, 41.5, 35.2, 31.1, 28.2, 26.9, 26.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930, 2096, 1737, 1654, 1476, 1371, 1309, 1206, 1141, 1105 cm^{-1}. HR-MS (ESI): calcd for $(C_{30}H_{37}O_6N_4)^+$ (M + H)$^+$: 549.2713; found, 549.2706.

Preparation of Tetrahydrocarbazolone 33. *(S)-4-[(4-Methoxyphenyl)oxy]cyclohex-2-en-1-one (****30****).* To a suspension of (*S*)-4-hydroxycyclohex-2-en-1-one (**29**)[26] (2.30 mg, 20.5 mmol, 1 equiv), magnesium oxide (1.66 g, 41.0 mmol, 2.00 equiv, vacuum-dried), and Dudley reagent II[14] (11.5 g, 41.0 mmol, 2.00 equiv) in α,α,α-trifluorotoluene (200 mL) was added dropwise methyl triflate (4.64 mL, 41.0 mmol, 2.00 equiv) at 0 °C. Upon completion of the addition, the reaction mixture was allowed to warm to 23 °C. After 75 min, ethyl acetate (40 mL) was added and the suspension was filtered through a fritted glass funnel. The filter cake was rinsed with ethyl acetate (2 × 20 mL). The filtrate was washed with water (50 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (9% to 14% ethyl acetate in hexanes) to afford **30** as a colorless oil (2.60 mg, 55%). The obtained characterization data were in full agreement with those values reported in the literature.[27]

*(S)-3-Bromo-4-[(4-methoxyphenyl)oxy]cyclohex-2-en-1-one (****27****).* (*S*)-4-[(4-Methoxyphenyl)oxy]cyclohex-2-en-1-one (**30**) (340 mg, 1.46 mmol, 1 equiv) was added to a mixture of sodium sulfate (643 mg, 4.53 mmol, 3.10 equiv) and *tert*-butyl carbazate (203 mg, 1.54 mmol, 1.05 equiv) in degassed 1,2-dichloroethane (1.2 mL) in a pressure flask. The resulting suspension was heated to 85 °C. After 4.5 h, the orange mixture was allowed to cool to 23 °C. Dichloromethane (4.4 mL) was added, the solution was cooled to 0 °C, and recrystallized *N*-bromosuccinimide (274 mg, 1.54 mmol, 1.05 equiv) was added. After 1 h at 0 °C, triethylamine (427 μL, 3.07 mmol, 2.10 equiv) was added in one portion. The resulting orange solution was stirred for 24 h at 23 °C. Acetone−water (v/v = 9:2, 6.1 mL) and Amberlyst 15 (1.76 g) were added, and the yellow suspension was heated to 50 °C. After 12 h, the reaction mixture was allowed to cool to 23 °C and then was diluted with dichloromethane (3 mL). The crude mixture was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford **27** as a yellow oil (261 mg, 57%). TLC (20% ethyl acetate in hexane): R_f = 0.32 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 2H), 6.94−6.87 (m, 2H), 6.48 (s, 1H), 4.68 (s, 2H), 4.26 (t, J = 4.7 Hz, 1H), 3.81 (s, 3H), 2.72−2.61 (m, 1H), 2.36 (dt, J = 16.9, 5.6 Hz, 1H), 2.23−2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 159.7, 149.4, 133.8, 129.8, 129.4, 114.0, 76.0, 72.6, 55.4, 33.2, 28.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2934, 2836, 1682, 1611, 1513, 1464, 1331, 1302, 1278, 1247, 1174, 1084 cm^{-1}. HR-MS (EI): calcd for $(C_{14}H_{15}{}^{79}BrO_3)^+$, 310.0199; found, 310.0200. $[\alpha]_{589}^{20}$ = −46.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

Enaminone ***31***. To an oven-dried pressure tube were added chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (126 mg, 0.18 mmol, 0.10 equiv), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (72 mg, 0.18 mmol, 0.10 equiv), sodium *tert*-butoxide (252 mg, 2.63 mmol, 1.50 equiv), 3,4-dimethoxyaniline (**15**) (402 mg, 2.63 mmol, 1.50 equiv), and toluene (12 mL). (*S*)-3-Bromo-4-[(4-methoxyphenyl)-oxy]cyclohex-2-en-1-one (**27**) (545 mg, 1.75 mmol, 1 equiv) was added, and the dark red suspension was heated to 80 °C for 18 h. The reaction mixture was allowed to cool to 23 °C and was filtered through a short plug of Celite. The filter cake was rinsed with dichloromethane (30 mL). The filtrate was concentrated and the residual red oil was

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purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford **31** as a brown foam (474 mg, 77%). TLC (2% methanol in dichloromethane): R_f = 0.22 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 2H), 6.98 (s, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.5, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.39 (s, 1H), 4.80 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.41 (dd, J = 11.4, 4.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.60−2.40 (m, 2H), 2.34 (ddd, J = 17.2, 13.4, 4.6 Hz, 1H), 1.99 (qd, J = 11.9, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 162.0, 159.9, 149.5, 147.3, 130.7, 129.9, 129.1, 116.8, 114.3, 111.5, 108.5, 97.9, 74.1, 71.4, 56.2, 56.1, 55.5, 35.1, 27.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3250, 2393, 1611, 1581, 1500, 1463, 1235, 1196, 1172, 1026 cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{25}NO_5)^+$, 383.1727; found, 383.1727. $[\alpha]_{589}^{20}$ = +12.8 (c = 0.31 × 10 g·mL^{-1}, CH_2Cl_2).

Tetrahydrocarbazolone ***32***. A solution of enaminone **31** (485 mg, 1.26 mmol, 1 equiv) in *N*,*N*-dimethylformamide (16 mL) was added to an oven-dried pressure tube containing palladium(II) acetate (28.4 mg, 0.13 mmol, 0.10 equiv), copper(II) acetate (689 mg, 3.79 mmol, 3.00 equiv), and potassium carbonate (524 mg, 3.79 mmol, 3.00 equiv). The resulting green-brown mixture was placed in a preheated oil bath at 140 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C, and the dark solution was filtered through a short plug of Celite. The filter cake was rinsed with dichloromethane (40 mL). The filtrate was concentrated. The residual black oil was purified by flash column chromatography on silica gel (50% to 66% ethyl acetate in hexanes) to afford **32** as a gray solid (275 mg, 57%). TLC (1% methanol in dichloromethane): R_f = 0.12 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.66 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 4.88 (dt, J = 8.8, 3.2 Hz, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.75 (dt, J = 15.5, 4.0 Hz, 1H), 2.60−2.46 (m, 2H), 2.29−2.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 159.6, 148.7, 147.8, 146.9, 130.1, 129.8, 129.7, 117.5, 114.2, 112.8, 103.1, 94.8, 71.0, 70.8, 56.3, 56.2, 55.4, 36.3, 30.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3294, 2949, 1626, 1585, 1540, 1513, 1466, 1340, 1295, 1247, 1135 cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{23}NO_5)^+$, 381.1571; found, 381.1570. Mp 196−199 °C. $[\alpha]_{589}^{20}$ = −1.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

N-Benzyltetrahydrocarbazolone ***33***. Tetrahydrocarbazolone **32** (203 mg, 0.532 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (2.7 mL), and the solution was cooled to 0 °C. Sodium hydride (25.5 mg, 0.639 mmol, 1.20 equiv, 60% dispersion in mineral oil) was added, and the suspension was stirred for 1 h at 0 °C. Benzyl bromide (76 μL, 0.639 mmol, 1.20 equiv) was added, and the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (60% ethyl acetate in hexanes) to afford **33** as a slightly beige solid (224 mg, 89%). Crystals that were suitable for X-ray diffraction analysis were obtained by crystallization from dichloromethane. TLC (50% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.67 (s, 1H), 7.27−7.22 (m, 3H), 7.14 (d, J = 8.4 Hz, 2H), 6.95 (dd, J = 6.7, 2.8 Hz, 2H), 6.84−6.76 (m, 2H), 6.64 (s, 1H), 5.22 (q, J = 16.7 Hz, 2H), 4.76 (t, J = 3.6 Hz, 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.43 (d, J = 11.1 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 2.88 (ddd, J = 16.4, 11.8, 4.4 Hz, 1H), 2.57−2.49 (m, 1H), 2.41 (dt, J = 16.6, 4.2 Hz, 1H), 2.26 (ddt, J = 15.0, 11.7, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 194.2, 160.0, 148.7, 147.8, 146.7, 137.1, 132.1, 130.3, 130.2, 129.3, 128.1, 126.7, 117.6, 114.3, 113.7, 103.8, 94.4, 71.1, 67.5, 56.6, 56.5, 55.8, 47.9, 34.3, 27.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 1700, 1647, 1558, 1540, 1513, 1483, 1444, 1303, 1270, 1248, 1173, 1106 cm^{-1}. HR-MS (ESI): calcd for $(C_{29}H_{29}NO_5)^+$, 471.2046; found, 471.2054. Mp 139−144 °C. $[\alpha]_{589}^{20}$ = −6.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

Preparation of Tetrahydrocarbazolone 34. *Tetrahydrocarbazolone* ***34***. *N*-Benzyltetrahydrocarbazolone **33** (49 mg, 0.10 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.12 mL, 0.12 mmol, 1.2 equiv) and hexamethylphosphoramide (36 μL, 0.20 mmol, 2.0 equiv) in tetrahydrofuran (0.5 mL) at −78 °C. After 1 h, methyl cyanoformate (12 μL, 0.15 mmol, 1.5 equiv) was added in one portion and the solution was slowly allowed to warm to 23 °C. After 20 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford the β-keto ester as a red oil (40 mg, 73%) containing minor impurities. The β-keto ester was used without additional purification for the next step.

Sodium hydride (2.5 mg, 62 μmol, 1.5 equiv, 60% suspension in mineral oil) was added a solution of the β-keto ester (22 mg, 41 μmol, 1 equiv) in *N*,*N*-dimethylformamide (0.4 mL) at 0 °C. After 1 h, ethyl iodide (13 μL, 0.16 mmol, 4.0 equiv) was added, the reaction flask was covered with aluminum foil, and the reaction mixture was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **34** as a brown oil (12 mg, 52%, dr = 4:1). All characterization data refer to the major diastereomer shown in the scheme. TLC (50% ethyl acetate in hexanes): R_f = 0.40 (UV, CAM). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.26−7.24 (m, 3H), 7.16−7.11 (m, 2H), 6.98−6.92 (m, 2H), 6.81−6.78 (m, 2H), 6.59 (s, 1H), 5.42−5.29 (m, 2H), 5.21 (dd, J = 7.7, 5.4 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.05 (dd, J = 13.3, 5.3 Hz, 1H), 2.29 (dd, J = 13.9, 7.5 Hz, 1H), 2.24 (dd, J = 13.2, 7.8 Hz, 1H), 2.09 (dd, J = 14.1, 7.3 Hz, 1H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 172.5, 159.6, 148.1, 147.3, 146.2, 136.5, 132.4, 129.8, 128.9, 127.7, 126.3, 117.8, 114.0, 112.7, 103.4, 93.8, 70.5, 68.9, 58.9, 56.3, 55.4, 52.7, 48.3, 36.0, 28.2, 9.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 2252, 1726, 1648, 1483, 1441, 1246, 1162, 1029 cm^{-1}, HR-MS (EI): calcd for $(C_{33}H_{35}NO_7)^+$, 557.2408; found, 557.2403.

Synthesis of the Tertiary Amine Building Block 14. *((2-Iodoethoxy)methyl)benzene* ***(37)***. 2-Benzyloxyethanol (5.00 g, 32.9 mmol, 1 equiv) was dissolved in dichloromethane (95 mL), and triphenylphosphine (12.9 g, 49.3 mmol, 1.50 equiv) and imidazole (3.36 g, 49.3 mmol, 1.50 equiv) were added. Iodine (12.5 g, 49.3 mmol, 1.5 equiv) was carefully added in three portions, and the yellow suspension was stirred at 23 °C. After 18 h, aqueous sodium thiosulfate solution (1 M, 100 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **37** (8.00 g, 93%) as a colorless oil. The obtained characterization data were in full agreement with those values reported in the literature.[20]

tert-Butyl N-Allyl-N-(2-benzyloxyethyl) Carbamate ***(38)***. *tert*-Butyl allylcarbamate (**36**) (3.14 g, 20.0 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (66 mL) and was added dropwise to a suspension of sodium hydride (1.20 g, 30.0 mmol, 1.50 equiv, 60% dispersion in mineral oil) in *N*,*N*-dimethylformamide (100 mL) at 0 °C. After 45 min, ((2-iodoethoxy)methyl)benzene (**37**) (6.81 g, 26.0 mmol, 1.30

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equiv) was added dropwise. The reaction mixture then was allowed to warm to 23 °C. After 16 h, the reaction mixture was carefully diluted with ammonium chloride solution (200 mL) and ethyl acetate (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **38** as a colorless oil (4.65 g, 80%). TLC (33% ethyl acetate in hexanes): R_f = 0.83 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.38−7.25 (m, 5H), 5.79 (dddd, J = 17.7, 9.8, 6.0, 5.2 Hz, 1H), 5.15−5.06 (m, 2H), 4.51 (s, 2H), 3.88 (br s, 2H), 3.58 (t, J = 5.9 Hz, 2H), 3.39 (br s, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 155.8, 139.3, 135.2, 128.8, 128.0, 128.0, 116.3, 116.0, 79.8, 73.4, 69.4, 51.3, 50.7, 46.9, 28.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976, 2930, 2861, 1690, 1477, 1454, 1405, 1365, 1244, 1173, 1150, 1103, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{26}NO_3)^+$ (M + H)$^+$, 292.1913; found, 292.1909.

*tert-Butyl N-(3-Hydroxypropyl)-N-(2-benzyloxyethyl) Carbamate (**39**).* *tert*-Butyl *N*-allyl-*N*-(2-benzyloxyethyl) carbamate (**38**) (3.1 g, 10.6 mmol, 1 equiv) was dissolved in tetrahydrofuran (5.6 mL), and a solution of 9-borabicyclo[3.3.1]nonane (0.5 M solution in tetrahydrofuran, 29.8 mL, 14.9 mmol, 1.40 equiv) was added at 0 °C. After 3 h at 0 °C, the reaction mixture was allowed to warm to 23 °C. After 16 h, aqueous sodium hydroxide solution (10 wt %, 4.9 mL) and aqueous hydrogen peroxide solution (30 wt %, 4.9 mL) were added dropwise and the reaction was heated to 50 °C. After 2 h, heating was ceased and the solution was allowed to cool to 23 °C. The reaction mixture was saturated with sodium carbonate, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **39** as a colorless oil (1.64 g, 50%). TLC (9% ethyl acetate in hexanes): R_f = 0.10 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.51 (s, 2H), 3.80 (t, J = 7.1 Hz, 1H), 3.67−3.31 (m, 8H), 1.87−1.59 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 138.1, 128.6, 127.9, 127.7, 80.4, 73.3, 68.8, 58.4, 47.3, 43.9, 30.7, 28.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3444, 2974, 2866, 1688, 1667, 1479, 1454, 1413, 1366, 1246, 1166, 1139, 1103 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{28}NO_4)^+$ (M + H)$^+$, 310.2018; found, 310.2015.

*tert-Butyl N-(3-Iodopropyl)-N-(2-benzyloxyethyl) Carbamate (**14**).* Iodine (541 mg, 2.13 mmol, 1.20 equiv) was added to a solution of triphenylphosphine (559 mg, 2.13 mmol, 1.20 equiv) and imidazole (145 mg, 2.13 mmol, 1.20 equiv) in dichloromethane (17.5 mL) at 0 °C. After 15 min, a solution of *tert*-butyl *N*-(3-hydroxypropyl)-*N*-(2-phenoxyethyl) carbamate (**39**) (550 mg, 1.78 mmol, 1 equiv) in dichloromethane (3.5 mL) was added dropwise. Upon completion of the addition, the yellow suspension was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with water (15 mL) and ethyl acetate (15 mL). The layers were separated, and the organic layer was washed with aqueous sodium thiosulfate solution (1 M, 40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **14** as a yellow oil (592 mg, 79%). TLC (20% ethyl acetate in hexanes): R_f = 0.68 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 4.52 (s, 2H), 3.68−3.51 (m, 2H), 3.49−3.37 (m, 2H), 3.34 (t, J = 7.0 Hz, 2H), 3.18−3.08 (m, 2H), 2.18−1.98 (m, 2H), 1.47 (s, 5H), 1.41 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ∼1:1 rotamer ratio, asterisk denotes signals of the second rotamer) δ 155.6, 138.3, *138.3, 132.5, *132.4, *128.6, 128.6, *127.8, 127.7, 80.0, *79.8, 73.2, 69.1, *69.0, 49.2, *47.9, 47.6, 40.6, 32.7, *32.5, 28.6, *28.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974, 1671, 1477, 1465, 1454, 1409, 1366, 1241, 1156, 1114 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{27}NO_3I)^+$ (M + H)$^+$, 420.1036; found, 420.1034.

Preparation of Tetrahydrocarbazolone 40. *Tetrahydrocarbazolone **40**.* *N*-Benzyltetrahydrocarbazolone **33** (50 mg, 0.11 mmol, 1 equiv) was dissolved in tetrahydrofuran (1.1 mL) and was added dropwise to a solution of lithium diisopropylamide (0.5 M in tetrahydrofuran, 320 μL, 0.16 mmol, 1.50 equiv; freshly prepared) at −78 °C. After 1 h, methyl cyanoformate (17 μL, 0.21 mmol, 2.00 equiv) was added in one portion and the solution was slowly allowed to warm to 23 °C. After 14 h, the red solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford β-keto ester as an orange oil (43 mg, dr = 2.5:1) which contained minor impurities. The β-keto ester was used without additional purification for the next step. To a suspension of sodium hydride (4.9 mg, 0.12 mmol, 1.5 equiv, 60% suspension in mineral oil) in *N*,*N*-dimethylformamide (0.4 mL) was added a solution of β-keto ester (43 mg, 0.08 mmol, 1 equiv) in *N*,*N*-dimethylformamide (0.8 mL) at 0 °C. After 30 min, *tert*-butyl *N*-(3-iodopropyl)-*N*-(2-phenoxyethyl) carbamate (**14**) (136 mg, 0.33 mmol, 4.00 equiv) was added, the reaction flask was covered with aluminum foil, and the reaction mixture was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% to 50% ethyl acetate in hexanes) to afford **40** as a yellow solid (54 mg, 60% over 2 steps). Partial separation of the diastereomeric mixture could be achieved by flash column chromatography on silica gel (25% ethyl acetate in hexanes). All characterization data refer to the major diastereomer shown in the scheme. TLC (50% ethyl acetate in hexanes): R_f = 0.28 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.79 (s, 1H), 7.34−7.27 (m, 5H), 7.27−7.21 (m, 3H), 7.15−7.11 (m, 2H), 6.96−6.92 (m, 2H), 6.81−6.78 (m, 2H), 6.60 (s, 1H), 5.34 (q, J = 16.5 Hz, 2H), 5.19 (dd, J = 7.9, 5.4 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.51 (s, 2H), 4.44 (d, J = 11.2 Hz, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 3.64−3.55 (m, 2H), 3.42 (t, J = 5.9 Hz, 2H), 3.36−3.25 (m, 3H), 3.02 (dd, J = 13.2, 5.5 Hz, 1H), 2.28−2.11 (m, 2H), 2.02 (td, J = 13.3, 12.6, 4.7 Hz, 1H), 1.63 (ddt, J = 31.4, 13.1, 6.2 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 189.3, 172.5, 159.8, 155.7, 148.4, 147.7, 146.3, 138.7, 136.6, 132.6, 129.9, 128.9, 128.5, 127.7, 126.4, 118.2, 114.2, 112.8, 103.9, 94.4, 79.5, 73.3, 70.5, 69.1, 69.0, 58.4, 56.5, 56.4, 55.5, 52.6, 48.5, 47.4, 36.8, 32.5, 28.7, 28.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1727, 1689, 1658, 1650, 1513, 1494, 1483, 1452, 1365 cm^{-1}. HR-MS (ESI): calcd for $(C_{48}H_{57}N_2O_{10})^+$, 821.4013; found, 821.4008. $[\alpha]_{589}^{20}$ = −3.6 (c = 0.5 × 10 g·mL^{-1}, CH_2Cl_2).

Preparation of Amine 42. *Amine **42**.* Tetrahydrocarbazolone **40** (13.5 mg, 16.4 μmol, 1 equiv) was added to a solution of hydrogen chloride in 1,4-dioxane (4 M, 0.1 mL) at 23 °C. After 2 h, the reaction mixture was diluted with saturated aqueous potassium carbonate solution (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (4% to 8% methanol in dichloromethane) to afford **41** (9.6 mg, quant.) which contained minor impurities. The product was used without additional purification for the next step. HR-MS (ESI): calcd for $(C_{35}H_{39}N_2O_6)^+$ (M + H)$^+$: 583.2808; found, 583.2805.

Preparation of Allyl Cyanoformate. *Allyl Cyanoformate.* Trimethylsilyl cyanide (1.98 g, 20.0 mmol, 1 equiv) was added to a suspension of allyl chloroformate (2.41 g, 20.0 mmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (12.30 mg, 0.110 mmol, 0.005 equiv) at 0

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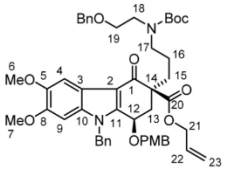
°C. The solution was allowed to warm to 23 °C. After 12 h, 1,4-diazabicyclo[2.2.2]octane was removed by filtration to afford allyl cyanoformate as a yellow oil (1.80 g, 81%). The product was used without further purification for the next step. The obtained characterization data were in full agreement with those values reported in the literature.[28]

Preparation of Diacylated Tetrahydrocarbazolone 45. *Diacylated Tetrahydrocarbazolone* ***45***. *N*-Benzyltetrahydrocarbazolone **33** (92 mg, 0.19 mmol, 1 equiv) was dissolved in tetrahydrofuran (2 mL) and was added dropwise to a solution of lithium diisopropylamide (freshly prepared from diisopropylamine (0.036 mL, 0.25 mmol, 1.3 equiv) and *n*-butyl lithium (2.3 M in hexanes, 0.10 mL, 0.23 mmol, 1.2 equiv)) in tetrahydrofuran (3 mL) at −78 °C. After 1 h, allyl chloroformate (0.041 mL, 0.39 mmol, 2.0 equiv) was added in one portion. The solution was allowed to warm to 23 °C. After 18 h, the reaction was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude material was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **45** as a yellow oil (30 mg, 24%). TLC (50% ethyl acetate in hexanes): R_f = 0.60 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27−7.20 (m, 3H), 7.19−7.10 (m, 2H), 6.87−6.78 (m, 4H), 6.59 (s, 1H), 5.94 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.80 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.36 (dq, J = 17.2, 1.6 Hz, 1H), 5.27−5.02 (m, 5H), 4.79−4.71 (m, 3H), 4.66 (d, J = 11.2 Hz, 1H), 4.64−4.50 (m, 2H), 4.37 (d, J = 11.2 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.28 (dd, J = 14.5, 3.7 Hz, 1H), 2.99 (dd, J = 14.4, 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 168.4, 168.1, 159.7, 148.4, 147.5, 144.9, 136.0, 132.0, 131.5, 130.5, 128.9, 127.9, 126.1, 118.7, 118.4, 117.6, 113.9, 112.1, 103.4, 93.6, 70.5, 66.8, 66.8, 65.1, 64.8, 56.3, 56.2, 55.4, 47.5, 34.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 1731, 1658, 1611, 1542, 1514, 1485, 1443, 1272, 1247, 1164, 1075, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{37}H_{38}NO_9)^+$ $(M + H)^+$, 640,2547; found, 640.2542.

Preparation of Tetrahydrocarbazolone 46.



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Tetrahydrocarbazolone ***46***. *N*-Benzyltetrahydrocarbazolone *ent*-**33** (10 mg, 0.020 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.5 mL), and hexamethylphosphoramide (0.040 mL, 0.040 mmol, 2.00 equiv) was added. A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.30 mL, 0.30 mmol, 1.5 equiv) was added dropwise at −78 °C. After 1 h, allyl cyanoformate (4.71 mg, 0.04 mmol, 2.00 equiv) was added in one portion. The solution was allowed to warm to 23 °C. After 13 h, the reaction was diluted with saturated aqueous sodium bicarbonate solution (2 mL) and ethyl acetate (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude material was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford β-keto ester **44** as a beige foam, which contained minor impurities. **44** was used without additional purification for the next step. To a solution of β-keto ester **44** (12 mg, 0.020 mmol, 1 equiv) and carbamate **7** (36.2 mg, 0.080 mmol, 4.0 equiv) in tetrahydrofuran (0.5 mL) was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.04 mL, 0.040 mmol, 2.0 equiv) dropwise over 15 min at −78 °C. The solution was allowed to warm to 23 °C. After 12 h, the reaction mixture was diluted with ethyl acetate (2 mL) and saturated aqueous sodium bicarbonate solution (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% to 50% ethyl acetate in hexanes) to afford **46** as a yellow oil (4.0 mg, 33% over 2 steps). TLC (50% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM). *Protons of diastereotopic methylene groups are reported as HA and HB, where HA is the more downfield shifted proton. In cases where resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g., the* ^{13}*C assignment "130.0 (PMB, Bn)" indicates that the resonance at 130.0 is either PMB or Bn).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H, H-4), 7.35−7.27 (m, 4H, Bn), 7.26−7.22 (m, 4H, Bn), 7.16−7.10 (m, 2H, PMB), 6.91−6.89 (m, 2H, Bn), 6.81−6.76 (m, 2H, PMB), 6.59 (s, 1H, H-9), 5.78 (ddt, $^3J_{22/23}$ = 17.2, $^3J_{22/23}$ = 10.4, $^3J_{22/21}$ = 5.5 Hz, 1H, H-22), 5.40 (d, $^2J_{HA/HB}$ = 16.6 Hz, 1H, Bn), 5.28 (d, $^2J_{HA/HB}$ = 16.6 Hz, 1H, Bn), 5.20−5.06 (m, 3H, H-12, H-23), 4.68 (app t, $^2J_{HA/HB}$ = 11.0 Hz, 1H, PMB), 4.54 (d, $^3J_{21/22}$ = 5.5 Hz, 2H, H-21), 4.51 (s, 2H, Bn), 4.42 (d, $^2J_{HA/HB}$ = 11.0 Hz, 1H, PMB), 3.94 (s, 3H, H-6), 3.78 (s, 3H, PMB), 3.76 (s, 3H, H-7), 3.63−3.52 (m, 2H, H-19), 3.41 (br s, 2H, H-18), 3.31 (br s, 2H, H-17), 3.03 (t, $^3J_{13/12}$ = 12.7 Hz, 1H, H_A-13), 2.31−2.09 (m, 3H, H_B-13, H-15), 1.66−1.56 (m, 2H, H-16), 1.43 (app d, J = 10.0 Hz, 9H, Boc). ^{13}C NMR (100 MHz, $CDCl_3$, asterisks denotes rotamer peaks) δ 189.3 (C-1), 171.5 (C-20), 159.6 (PMB), 155.7 (Boc), 155.5* (Boc), 148.1 (C-8), 147.3 (C-5), 146.1 (C-11), 145.9* (C-11), 138.5 (Bn), 136.4 (Bn), 132.4 (C-10), 131.7 (C-22), 130.0 (PMB, Bn), 129.8 (PMB, Bn), 129.2 (PMB), 128.9 (Bn), 128.5 (Bn), 127.6 (Bn), 126.2 (Bn), 118.5 (C-3, C-23), 117.7 (C-3, C-23), 114.0 (PMB), 112.7 (C-2), 103.3 (C-4), 93.7 (C-9), 79.5 (Boc), 73.1 (Bn), 70.3 (PMB), 69.0 (C-12), 68.7 (C-19), 65.9 (C-21), 58.3 (C-14), 56.3 (C-6), 56.2 (C-7), 55.4 (PMB), 48.2 (Bn), 47.2 (C-17), 47.0 (C-18), 36.5 (C-13), 32.3 (C-15), 32.1* (C-15), 28.6 (Boc), 24.2 (C-16), 23.7* (C-16). IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2932, 1728, 1689, 1513, 1453, 1411, 1365, 1248, 1163, 1103, 1067, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{50}H_{59}N_2O_{10})^+$ $(M + H)^+$, 847.4170; found, 847.4155.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01095.

Experimental procedures, X-ray crystallographic data for **33**, NMR spectra of products (PDF)

Crystallographic data for **33** (CIF)

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Notes

The authors declare no competing financial interest.

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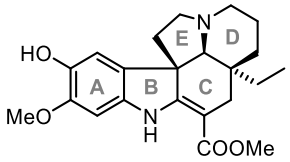
J. Org. Chem. 2017, 82, 7410−7419

8 Summary

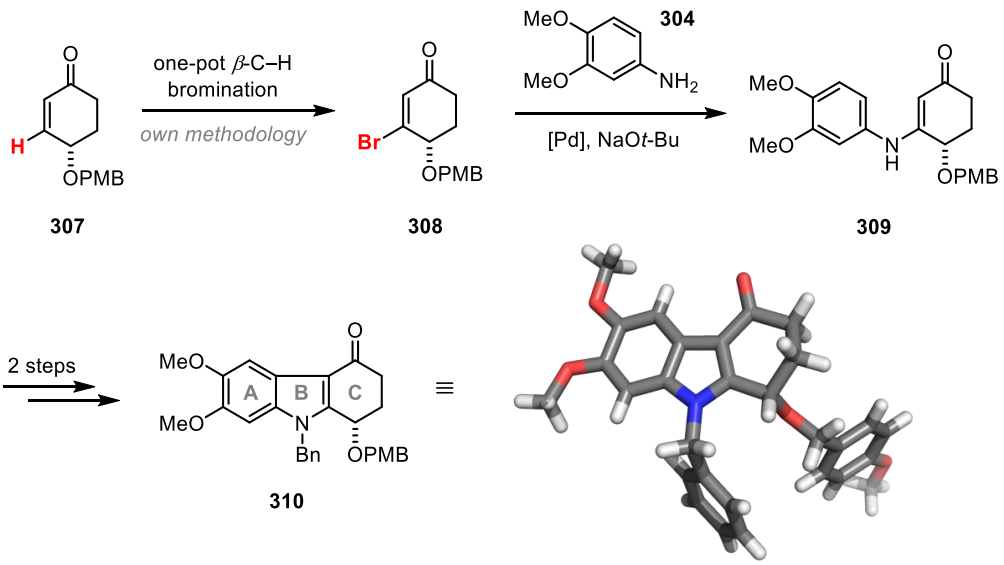
The *Aspidosperma* alkaloids are a large family of secondary metabolites isolated from plants with fascinating structures and remarkable biological activities. The jerantinines are members of this family that have been isolated in 2008. They were found to be microtubule disrupting agents (MDA) and could find use as anti-cancer agents in the future. Jerantinine E (**256**) has been already synthetically accessed in 2013 and our goal was to shorten the synthesis of its core structure by employing our previously developed one-pot procedure for the selective *β*-C−H bromination of cyclic enones.



jerantinine E
(**256**)

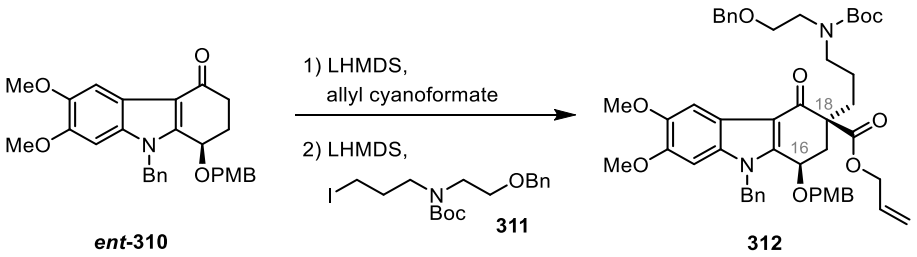
Figure 9. The *Aspidosperma* alkaloid jerantinine E (**256**).

Thus, the successful development of a short and convergent synthesis of the core structure of jerantinine E (**256**) has been detailed in the second part of this thesis. The use of an enone building block with a CH_2OBn substituent in *γ*-position, as described earlier, had to be revised due to base induced elimination of the benzyl ether under various alkylation conditions. Instead, an enantiopure *γ*-hydroxylated enone could be utilized. Starting with the *β*-bromination of PMB protected enone **307** by using our own methodology, *β*-bromo enone **308** was obtained (Scheme 81). The indole substructure was then constructed via Buchwald−Hartwig amination with 3,4-dimethoxyaniline (**304**) and by subsequent palladium-catalyzed oxidative indole formation to afford the tricyclic tetrahydrocarbazolone core structure **309** of the natural product. Benzylation of the indole fragment gave tricycle **310**, whose structure was further proven by single crystal X-ray analysis.



Scheme 81. Synthesis of the tricyclic tetrahydrocarbazolone core **310**) of jerantinine E (**256**) and its molecular structure.

With an established route for the tetrahydrocarbazolone core in hand, functionalization of the C ring for the installation of the D and E ring was investigated. Therefore, various alkylation procedures were extensively examined. Unfortunately, direct alkylation of tetrahydrocarbazolone **310** was found to be challenging. Thus, ketone ***ent*-310** was converted to its allyl β-keto ester, which was then alkylated with readily prepared alkyl iodide **311**. The stereocenter at C16 thereby directed the alkylation reaction. A diastereoselective palladium-catalyzed decarboxylative allylation reaction should later set the quaternary stereocenter at C18. This two-step procedure gave functionalized tetrahydrocarbazolone **312**, which contained all carbon atoms of the D and E ring of jerantinine E (**256**) (Scheme 82).



Scheme 82. Functionalization of the tetrahydrocarbazolone core ***ent*-310** by acylation and subsequent alkylation.

In future studies, a thorough screening of reaction conditions such as catalysts, ligands, solvents and temperatures will be required for the realization of the palladium-catalyzed decarboxylative allylation.

Experimental Part

9 Experimental Section for Part I

9.1 General Experimental Details

9.1.1 General Working Methods

All reactions were performed in glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. All glassware was dried in an oven at 130 °C prior to use. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas or were dissolved in appropriate solvents. High pressure reactions were conducted in a miniclave steel apparatus from *BÜCHI AG*. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above 23 °C were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using glass plates precoated with silica gel (0.25 mm, 60 Å pore size, *Merck*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous basic potassium permanganate solution ($KMnO_4$), aqueous acidic ceric ammonium molybdate solution (CAM), or an aqueous acidic *p*-anisaldehyde solution and were developed by heating with a heat gun. Flash-column chromatography on silica gel was performed as described by Still *et al.*,[159] employing silica gel (60 Å, 40–63 μm, *Merck KGaA*). Flash column chromatography on silica gel using triethylamine pretreated silica gel was performed by preparing the silica gel slurry with triethylamine (7.5% v/v in corresponding eluent mixture) and flushing the column with the eluent prior to loading the compound on the column. The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

9.1.2 Solvents and Reagents

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled under nitrogen atmosphere from calcium hydride prior to use. Benzene (PhH), Chlorobenzene (PhCl), toluene (PhMe), 1,4-dioxane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (MeCN), ethanol (EtOH) and methanol (MeOH) were purchased from *Acros Organics* as 'extra dry' reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (*Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, TCI Europe, carbolution, ABCR*) and were used as received. Solvents for extraction, crystallization and flash column chromatography on silica gel

were purchased in technical grade and distilled under reduced pressure prior to use. Lithium chloride and lithium bromide were dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 130 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. 4 Å molecular sieves were washed (methanol, acetone, dichloromethane) and then dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 130 °C (760 mmHg); the molecular sieves were flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[160]

9.1.3 NMR Spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 800 MHz spectrometer equipped with a CryoProbeTM, *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbeTM, *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 800 MHz, 400 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (200 MHz, 100 MHz, 75 MHz, 100 MHz, 150 MHz for carbon nuclei), respectively. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, $CDHCl_2$: δ 5.32, C_6HD_5: 7.16). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_2Cl_2: δ 54.00, C_6D_6: 128.06, acetone-d_6: 29.84). ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton) (e.g. "5.21 (t, $^3J_{9/8}$ = 7.3 Hz, 1H, H-9)"). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), se (sextet), h (heptet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Protons of diastereotopic methylene groups are reported as H-Xa and H-Xb, where H-Xa is the more downfield shifted proton. The nomenclature is arbitrarily and does not correspond to the spin system. Furthermore, the numbering of the proton and carbon atoms does not correspond to the IUPAC nomenclature. ^{13}C NMR spectroscopic data are reported as follows: Chemical shift in ppm (assigned carbon) (e.g. "159.22 (C-21)"). In cases were resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g. the ^{13}C NMR assignment "18.29 (C-16, C-17), 17.84 (C-16, C-17)" indicates that the resonance at 18.29 is either C-16 or C-17). In addition to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal

assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. All raw FID files were processed and the spectra analyzed using the program *MestReNova 9.0.1* from *Mestrelab Research S. L*.

9.1.4 Mass Spectrometry

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionisation mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan gmbH*. Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

9.1.5 IR Spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. Data are represented in frequency of absorption (cm^{-1}).

9.1.6 Optical Rotation

Optical rotation values were recorded on a *PerkinElmer 241* or *Anton Paar MCP 200* polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{\alpha}{\beta \cdot d}$$

α: recorded optical rotation

β: concentration of the analyte in 10 mg/mL

d: length of the cuvette in dm

φ: measuring temperature in °C

λ: wave length in nm

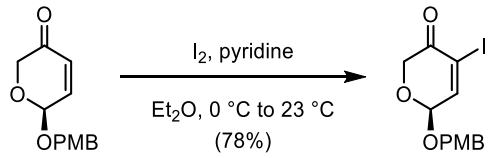
The respective concentration and the solvent are denoted in the analytical part of the experimental description.

9.1.7 Melting Point Ranges

Melting point ranges were measured on a B-540 melting point apparatus from *BÜCHI Labortechnik AG* and are uncorrected.

9.2 Experimental Procedures

9.2.1 Experimental Procedures for Chapter 3.1



20 **29**

***α*-Iodo enone 29.** Pyridine (25 mL) was added to a solution of iodine (5.08 g, 20.0 mmol, 2.00 equiv) in diethyl ether (25 mL) at 23 °C. The solution was cooled to 0 °C and stirred in the dark. After 20 min, (*S*)-6-(4-methoxybenzyl)oxy-2*H*-pyran-3(6*H*)-one[39] (**20**) (2.35 g, 10.0 mmol, 1 equiv) was added. After 75 min, the reaction mixture was allowed to warm to 23 °C. After 1.5 h, the reaction mixture was diluted with aqueous sodium thiosulfate solution (0.1 M, 180 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (4×100 mL). The combined organic layers were washed with aqueous copper(II) sulfate solution (1 M, 100 mL), water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% to 15% ethyl acetate in hexanes) to yield **29** (2.79 g, 78%) as light yellow crystals.

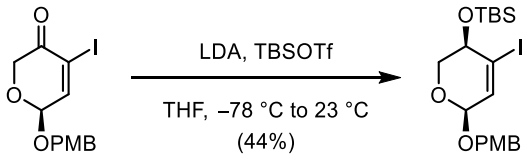
TLC (10% ethyl acetate in hexanes), R_f = 0.19 ($KMnO_4$, UV).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, *J* = 3.7 Hz, 1H), 7.30–7.27 (m, 2H), 6.94–6.87 (m, 2H), 5.16 (d, *J* = 3.7 Hz, 1H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 16.7 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.34 (d, *J* = 16.6 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 188.2, 159.9, 153.3, 130.2, 128.6, 114.3, 103.0, 94.0, 78.7, 65.9, 55.5.

HRMS (EI): calcd for $(C_{13}H_{13}IO_4)^+$: 359.9853; found: 359.9845.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3048, 2927, 2833, 1705, 1606, 1516, 1328, 1305, 1251, 1177, 1131, 1019 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = –9.1 (c = 1.2 · 10 g · mL^{-1}, CH_2Cl_2).



29 **18**

Vinyl iodide 18. *n*-Butyllithium (2.3 M in hexanes, 0.180 mL, 0.420 mmol, 1.20 equiv) was added to a solution of diisopropylamine (59.4 μL, 0.420 mmol, 1.20 equiv) in tetrahydrofuran (1 mL) at –78 °C and the reaction mixture was stirred for 10 min at –78 °C and then 20 min at 0 °C. The reaction mixture was cooled to –78 °C and a solution of *α*-iodo enone **29** (126 mg, 0.35 mmol, 1 equiv) in tetrahydrofuran (0.7 mL) was added dropwise. After 45 min, *t*-butyldimethylsilyl trifluoromethanesulfonate (121 μL, 0.53 mmol, 1.50 equiv) was added. After 1 h, the solution was allowed to warm to 23 °C. After 1 h at 23 °C, saturated ammonium chloride solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes) to provide **18** (73 mg, 44%) as a light yellow solid.

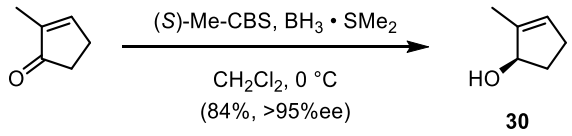
TLC (5% diethyl ether in hexanes): R*f* = 0.26 (CAM, UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.94–6.84 (m, 2H), 6.43 (dt, *J* = 3.0, 1.4 Hz, 1H), 4.84 (d, *J* = 3.1 Hz, 1H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.19 (ddd, *J* = 9.4, 5.9, 1.6 Hz, 1H), 3.89–3.76 (m, 5H), 0.93 (d, *J* = 1.1 Hz, 9H), 0.21 (d, *J* = 1.1 Hz, 3H), 0.11 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 136.5, 129.8, 129.6, 114.0, 110.6, 94.6, 69.6, 68.1, 63.7, 55.4, 26.0, 18.3, –4.1, –4.3.

HRMS (ESI): calcd for $(C_{11}H_{20}IO_2Si)^+$ $(M–C_8H_9O_2)^+$: 339.0277; found: 339.0274.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928, 2856, 1613, 1514, 1463, 1352, 1251, 1174, 1119, 1061, 1053 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +7.5 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



30

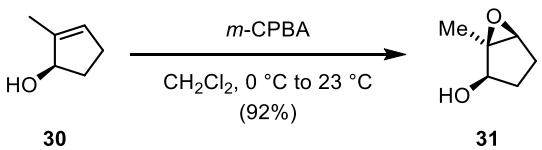
(*R*)-2-Methyl-2-cyclopenten-1-ol (30). (*S*)-(–)-Methyl-CBS-oxazaborolidine (4.45 g, 15.8 mmol, 1.05 equiv, neat, 98% purity) was dissolved in dichloromethane (60 mL) and borane-methylsulfide complex (1.20 g, 15.8 mmol, 1.05 equiv) was added. The solution was cooled to 0 °C and a solution of 2-methyl-2-cyclopenten-1-one (1.47 g, 15.0 mmol, 1 equiv) in dichloromethane (30 mL) was added dropwise over 1.5 h via syringe pump. Upon completion of the addition, stirring was continued for 30 min. The mixture was then carefully diluted with methanol (8 mL) and the solution was allowed to warm to 23 °C. Water (20 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated (Caution, the compound is volatile! Vacuum > 600 mbar, water bath: 35 °C). The crude product was purified by flash column chromatography on silica gel (33% diethyl ether in pentane) to afford **30** (1.23 g, 84%, >95% ee as determined by Mosher analysis using ^{19}F spectroscopy) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55–5.50 (m, 1H), 4.63–4.54 (m, 1H), 2.45–2.25 (m, 2H), 2.24–2.13 (m, 1H), 1.78 (s, 3H), 1.69 (ddt, *J* = 13.2, 8.8, 4.4 Hz, 1H), 1.47–1.38 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.9, 128.3, 80.1, 34.2, 29.9, 13.7.

HR-MS (EI): calcd for $(C_6H_{10}O)^+$: 98.0732, found: 98.0726.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3320, 3040, 2963, 2938, 2915, 2854, 2239, 1448, 1437, 1377, 1333, 1313, 1164, 1052, 1029 cm^{-1}.

$[\alpha]_{589}^{21}$ = +40.8 (c = 1.00 · 10 g · mL^{-1}, CH_2Cl_2).



30 **31**

***(1R,2R,5S)*-1-Methyl-6-oxabicyclo[3.1.0]hexan-2-ol (31)**. (*R*)-2-Methyl-2-cyclopenten-1-ol (**30**) (1.68 g, 17.1 mmol, 1 equiv) was dissolved in dichloromethane (100 mL) and the solution was

cooled to 0 °C. 3-Chloroperbenzoic acid (25.7 mmol, 5.76 g, 1.50 equiv, 75% purity) was added in two portions and upon completion of the addition, the suspension was allowed to warm to 23 °C. After 2 h, the solution was diluted with saturated aqueous sodium thiosulfate solution (100 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (3×90 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated (vacuum > 580 mbar, water bath: 35 °C). The residue was purified by flash column chromatography on silica gel (50% to 66% diethyl ether in pentane) to afford **31** (1.79 g, 92%) as a colorless oil.

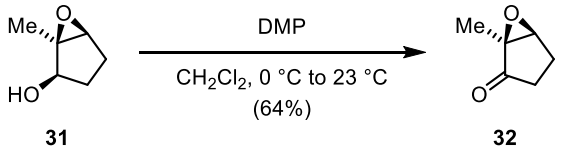
TLC (50% ethyl acetate in hexanes): R_f = 0.33 (Anis).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.00 (t, *J* = 7.9 Hz, 1H), 3.27–3.23 (m, 1H), 1.98–1.87 (m, 3H), 1.59 (dddd, *J* = 14.2, 10.5, 8.4, 1.3 Hz, 1H), 1.44 (s, 3H), 1.30–1.18 (m, 1H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 75.9, 65.5, 63.2, 29.3, 25.5, 14.8.

HR-MS (EI): calcd for $(C_6H_{10}O_2)^+$: 114.0681, found: 114.0672.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3405, 2952, 1438, 1335, 1067, 993, 949 cm^{-1}.

$[\alpha]_{589}^{21}$ = –10.8 (c = 0.95 · 10 g · mL^{-1}, CH_2Cl_2).



31 **32**

(*1S,5S*)-1-Methyl-6-oxabicyclo[3.1.0]hexan-2-one (32). To a solution of (*1R,2R,5S*)-1-methyl-6-oxabicyclo[3.1.0]hexan-2-ol (**31**) (1.79 g, 15.7 mmol, 1 equiv) in dichloromethane (79 mL) was added Dess–Martin periodinan (9.31 g, 22.0 mmol, 1.40 equiv) at 0 °C. The solution was allowed to warm to 0 °C. After 3 h, the solution was diluted with saturated aqueous sodium thiosulfate solution (100 mL) and dichloromethane (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×90 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (50% diethyl ether in pentane) to afford **32** (1.12 g, 64%) as a colorless oil.

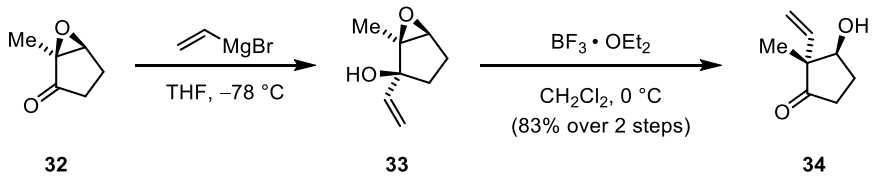
TLC (50% diethyl ether in pentanes): R_f = 0.42 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (d, *J* = 1.6 Hz, 1H), 2.43–2.21 (m, 2H), 2.18–2.05 (m, 1H), 2.03–1.93 (m, 1H), 1.44 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.0, 64.3, 61.1, 31.3, 22.4, 10.1.

HR-MS (EI): calcd for $(C_6H_8O_2)^+$: 112.0524, found: 112.0522.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1737, 1445, 1407, 1374, 1092, 1069, 967, 542 cm^{-1}.

$[\alpha]_{589}^{21}$ = –34.9 (c = 0.18 · 10 g · mL^{-1}, CH_2Cl_2).



32 **33** **34**

Ketone 34. To a solution of (*1S,5S*)-1-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**32**) (1.12 g, 9.99 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added a solution of vinylmagnesium bromide (1.0 M in tetrahydrofuran) dropwise via syringe pump at –78 °C. After 1 h, the solution was diluted with saturated aqueous ammonium chloride solution (50 mL) and the suspension was allowed to warm to 25 °C. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with saturated aqueous ammonium chloride solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was used without further purification for the next step.

Crude **33** (assumed: 1.40 g, 9.99 mmol, 1 equiv) was dissolved in dichloromethane (59 mL) and the solution was cooled to 0 °C. Borontrifluoride etherate (5.25 mL, 20.0 mmol, 2.00 equiv, 47% in diethyl ether) was added dropwise. After 1 h, saturated aqueous sodium bicarbonate solution (25 mL) was added dropwise at 0 °C. Upon completion of the addition, one spatula of solid sodium bicarbonate was added and the suspension was allowed to warm to 25 °C. When gas evolution deceased, the layers were separated and the aqueous layer was extracted with dichloromethane (3×80 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (80 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated (vacuum >550 mbar, water bath: 35 °C). The crude product was purified by flash column chromatography on silica gel (33% to 50% diethyl ether in pentanes) to afford **34** (1.16 g, 83%) as a colorless oil.

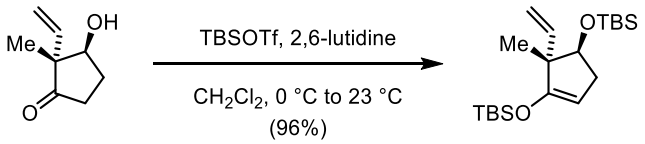
TLC (50% ethyl acetate in hexanes): R_f = 0.50 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.17 (dd, *J* = 10.7, 0.7 Hz, 1H), 5.11 (dd, *J* = 17.5, 0.7 Hz, 1H), 4.30–4.25 (m, 1H), 2.53–2.41 (m, 1H), 2.33–2.20 (m, 2H), 2.00–1.89 (m, 1H), 1.79 (d, *J* = 3.5 Hz, 1H), 1.14 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 218.1, 138.6, 116.3, 76.8, 57.6, 34.4, 27.8, 15.5.

HR-MS (EI): calcd for $(C_8H_{12}O_2)^+$: 140.0837, found: 140.0832.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3440, 2975, 1731, 1631, 1450, 1407, 1368, 1261, 1217, 1182, 1066 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{21}$ = +11.7 (c = 0.75 · 10 g · mL^{-1}, CH_2Cl_2).



34 **19**

TBS enol ether 19. 2,6-Lutidine (0.48 mL, 4.10 mmol, 4.10 equiv) was added to a solution of ketone **34** (80% solution in diethyl ether, 159 mg, 1.00 mmol, 1 equiv) in dichloromethane (5 mL) at 0 °C. *Tert*-butyldimethylsilyl trifluoromethanesulfonate (0.47 mL; 2.05 mmol, 2.05 equiv) was then added dropwise. Upon completion of the addition, the solution was allowed to warm to 23 °C. After 30 min, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and dichloromethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (hexanes) to afford **19** (352 mg, 96%) as a colorless oil.

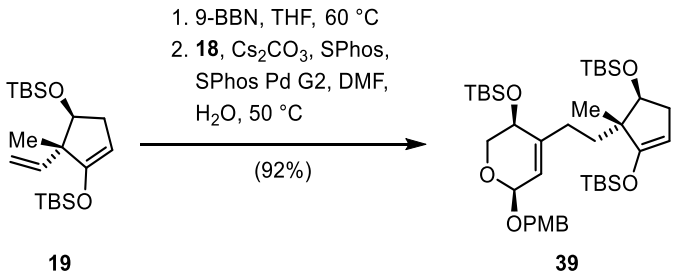
TLC (hexanes): R_f = 0.70 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.04 (d, *J* = 4.3 Hz, 1H), 5.01 (s, 1H), 4.43–4.36 (m, 1H), 4.09 (t, *J* = 6.8 Hz, 1H), 2.40 (ddd, *J* = 14.5, 7.2, 2.8 Hz, 1H), 2.08 (ddt, *J* = 14.4, 6.6, 1.4 Hz, 1H), 1.04 (s, 3H), 0.89 (s, 9 H), 0.87 (s, 9H), 0.13 (s, 6H), 0.01 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.6, 144.1, 113.3, 96.5, 78.0, 53.3, 35.9, 26.0, 25.8, 18.3, 18.2, 15.5, −4.4, −4.5, −4.6, −4.8.

HR-MS (EI): calcd. for $(C_{20}H_{40}O_2Si_2)^+$: 368.2567, found: 368.2561.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956, 2930, 1640, 1472, 1463, 1251, 1239, 1099 cm^{-1}.

$[\alpha]_{589}^{21}$ = +21.3 (c = 0.83 · 10 g · mL^{-1}, CH_2Cl_2).



Alkene 39. To a solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (0.5 M, 1.64 mL, 0.820 mmol, 1.95 equiv) was added dropwise a solution of alkene **19** (232 mg, 0.420 mmol, 1.50 equiv) in tetrahydrofuran (2.5 mL) at 25 °C. The solution was heated to 60 °C. After 3 h 45 min, heating was ceased and the solution was allowed to cool to 25 °C. In a separate flask, cesium carbonate (287 mg, 0.880 mmol, 2.10 equiv), SPhos Pd g2 (15 mg, 21 µmol, 0.05 equiv), SPhos (8.6 mg, 21 µmol, 0.05 equiv) and vinyl iodide **18** (200 mg, 0.420 mmol, 1 equiv) were dissolved in a mixture of degassed dimethylformamide and water (v/v = 9:1, 4.7 mL). The solution of the generated borane was added dropwise and complete transfer was ensured by using an additional 0.5 mL of degassed tetrahydrofuran. The orange solution was heated to 50 °C. After 2 h, heating was ceased and the solution was allowed to cool to 25 °C. The solution was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford **39** (278 mg, 92%) as a colorless oil.

TLC (3% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM).

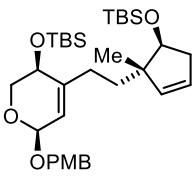
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H), 6.96–6.81 (m, 2H), 5.44–5.34 (m, 1H), 5.01–4.92 (m, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.36–4.29 (m, 1H), 4.20–4.14 (m, 1H), 4.07 (dd, *J* = 7.4, 5.9 Hz, 1H), 3.80 (s, 3H), 3.76–3.63 (m, 2H), 2.37 (dddd, *J* = 14.4, 7.4, 4.2, 2.5 Hz, 1H), 2.30–2.21 (m, 1H), 2.03 (dddd, *J* = 16.5, 8.6, 4.5, 2.2 Hz, 1H), 1.86–1.73 (m, 1H), 1.48–1.37 (m, 2H), 0.92 (s, 3H), 0.90–0.86 (m, 27H), 0.14–0.12 (m, 6H), 0.09–0.06 (m, 6H), 0.03–0.00 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.4, 157.9, 146.3, 130.4, 129.9, 129.8, 118.6, 114.0, 95.8, 94.0, 75.1, 69.3, 66.5, 63.1, 55.4, 50.0, 36.4, 33.1, 26.0, 25.9, 25.8, 18.2, −4.1, −4.1, −4.5, −4.6, −4.8, −4.9.

HR-MS (ESI): calcd for $(C_{31}H_{61}O_4Si_3)^+$ $(M–C_8H_9O_2)^+$: 581.3878, found: 581.3884.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956, 2929, 1640, 1614, 1514, 1472, 1463, 1362, 1337, 1250, 1095, 1077, 1029, 1007 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{21}$ = +14.1 (c = 0.51 · 10 g · mL^{-1}, CH_2Cl_2).

Sideproduct 38.



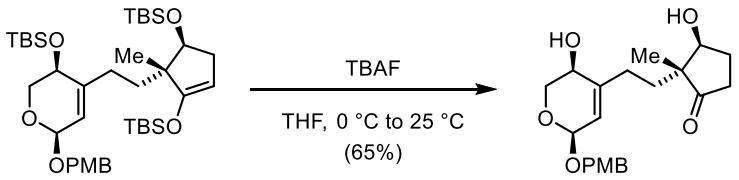
TLC (3% ethyl acetate in hexanes): R_f = 0.15 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 6.91–6.85 (m, 2H), 5.57–5.49 (m, 2H), 5.39 (dq, *J* = 3.2, 1.6 Hz, 1H), 4.99–4.94 (m, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.26–4.19 (m, 1H), 4.00 (dd, *J* = 7.1, 6.0 Hz, 1H), 3.80 (s, 3H), 3.75–3.66 (m, 2H), 2.49 (dddd, *J* = 16.1, 7.1, 2.5, 1.6 Hz, 1H), 2.20 (ddt, *J* = 16.2, 6.0, 2.0 Hz, 1H), 2.16–2.08 (m, 1H), 2.07–1.99 (m, 1H), 1.50 (td, *J* = 12.9, 4.6 Hz, 1H), 1.39–1.30 (m, 1H), 0.93 (s, 3H), 0.89 (d, *J* = 3.5 Hz, 18H), 0.10 (s, 3H), 0.08 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.4, 146.3, 138.5, 130.3, 129.8, 126.33, 119.4, 114.0, 93.9, 78.7, 69.4, 66.0, 63.0, 55.4, 50.7, 40.7, 37.0, 26.6, 26.0, 25.9, 19.2, 18.3, 18.2, −3.9, −4.2, −4.7.

HR-MS (ESI): calcd. for $(C_{33}H_{60}O_5NSi_2)^+$ $(M+NH_4)^+$: 606.4010, found: 606.4023.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956, 2929, 2857, 1613, 1514, 1463, 1361, 1251, 1111, 1076, 1034 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{21}$ = +35.0 (c = 1.0· 10 g · mL^{-1}, CH_2Cl_2).



38 **44**

Diol 44. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 2.0 mL, 2.0 mmol, 5.0 equiv) was added dropwise to a solution of alkene **38** (289 mg, 0.400 mmol, 1 equiv) in tetrahydrofuran (4.1 mL) at 0 °C. Upon completion of the addition, the solution was allowed to warm to 25 °C. After 14 h, the solution was diluted with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (ethyl acetate) to afford **44** (98 mg, 65%) as a colorless oil.

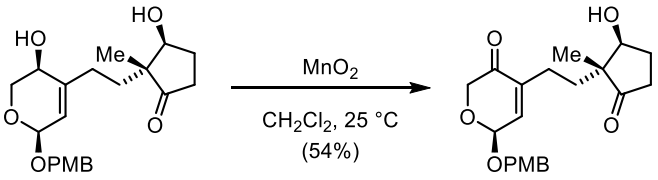
TLC (ethyl acetate): R_f = 0.41 (UV, CAM).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 6.90–6.84 (m, 2H), 5.48–5.45 (m, 1H), 4.99–4.96 (m, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.23–4.16 (m, 1H), 4.11–4.05 (m, 1H), 3.80 (s, 3H), 3.77 (d, *J* = 6.2 Hz, 2H), 2.48–2.41 (m, 1H), 2.33 (s, 1H), 2.27–2.15 (m, 3H), 2.12–2.05 (m, 1H), 1.87–1.80 (m, 2H), 1.66 (ddd, *J* = 13.9, 11.2, 5.0 Hz, 1H), 1.57 (ddd, *J* = 14.0, 11.4, 5.4 Hz, 1H), 0.99 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 221.0, 159.5, 143.7, 129.9, 129.9, 122.4, 114.0, 94.5, 75.2, 69.7, 65.3, 64.3, 55.4, 53.1, 35.2, 32.4, 27.8, 26.7, 15.4.

HR-MS (ESI): calcd for $(C_{21}H_{28}O_6Na)^+$ $(M+Na)^+$: 399.1784, found: 399.1785.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3423, 2963, 1732, 1612, 1214, 1463, 1248, 1174, 1067, 1029 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{21}$ = +1.5 (c = 0.54 · 10 g · mL^{-1}, CH_2Cl_2).



44 **45**

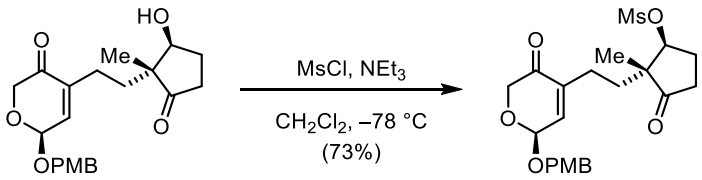
Enone 45. Activated manganese(IV) oxide (754 mg, 7.81 mmol, 30.0 equiv) was added to a solution of diol **44** (98 mg, 0.26 mmol, 1 equiv) in dichloromethane (2.7 mL) at 25 °C. After 1 h 30 min, the suspension was filtered through a short plug of celite and the filter cake was rinsed with dichloromethane. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **45** (52.5 mg, 54%) as a colorless oil.

TLC (50% ethyl acetate in hexanes): R_f = 0.50 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 6.93–6.87 (m, 2H), 6.60–6.57 (m, 1H), 5.26 (dq, *J* = 3.5, 0.7 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.45 (dd, *J* = 16.9, 0.6 Hz, 1H), 4.27–4.20 (m, 1H), 4.08 (dd, *J* = 16.9, 0.7 Hz, 1H), 3.81 (d, *J* = 0.7 Hz, 3H), 2.52–2.39 (m, 1H), 2.31–2.14 (m, 4H), 1.93–1.82 (m, 1H), 1.78 (d, *J* = 4.4 Hz, 1H), 1.58–1.45 (m, 2H), 1.02 (d, *J* = 0.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 219.6, 194.9, 159.6, 139.1, 138.6, 129.9, 129.0, 114.0, 92.7, 75.4, 75.4, 70.3, 66.2, 55.3, 52.8, 34.8, 33.0, 27.7, 22.5, 14.7.

HR-MS (ESI): calcd. for $(C_{21}H_{26}O_6Na)^+$ $(M+Na)^+$: 397.1627, found: 397.1626.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3470, 2934, 1734, 1689, 1612, 1514, 1464, 1339, 1303, 1249, 1174, 1032 cm^{-1}.



45 **48**

Mesylate 48. Triethylamine (17 µL, 0.12 mmol, 2.1 equiv) and mesyl chloride (7.0 µL, 88 µmol, 1.5 equiv) was added to a solution of enone **45** (22 mg, 59 µmol, 1 equiv) in dichloromethane (1 mL) at –78 °C. After 3.5 h, the solution was diluted with saturated aqueous sodium chloride (10 mL) and dichloromethane (10 mL). The layers were separated and the aqueous layer was

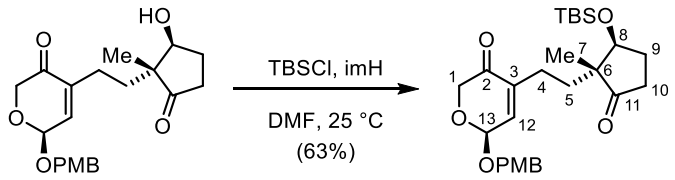
extracted with dichloromethane (3×15 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **48** (19.5 mg, 73%) as a colorless oil

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32–7.24 (m, 2H), 6.93–6.84 (m, 2H), 6.61 (dt, *J* = 3.6, 1.3 Hz, 1H), 5.27 (dd, *J* = 3.6, 0.8 Hz, 1H), 5.10 (t, *J* = 5.5 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.43 (dd, *J* = 16.8, 0.3 Hz, 1H), 4.05 (d, *J* = 16.8 Hz, 1H), 3.79 (s, 3H), 3.06 (s, 3H), 2.55–2.38 (m, 2H), 2.34–2.10 (m, 4H), 1.63–1.48 (m, 2H), 1.07 (s, 3H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 216.6, 195.2, 160.2, 140.1, 138.5, 130.4, 129.9, 114.4, 93.7, 84.8, 70.9, 66.8, 55.8, 52.9, 39.1, 35.0, 33.5, 26.8, 23.2, 16.3.

HR-MS (ESI): calcd for $(C_{14}H_{19}O_6S)^+$ $(M–C_8H_9O_2)^+$: 315.0902, found: 315.0903.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2933, 2892, 1742, 1689, 1612, 1515, 1464, 1354, 1303, 1249, 1176, 1032 cm^{-1}.

$[\alpha]_{589}^{21}$ = –21.7 (c = 0.29 · 10 g · mL^{-1}, CH_2Cl_2).



45 **47**

TBS ether 47. *Tert*-butyldimethylchlorosilane (9.5 mg, 63 µmol, 2.0 equiv) was added to a solution of enone **45** (11.8 mg, 31.5 µmol, 1 equiv) and imidazole (2.4 mg, 35 µmol, 1.1 equiv) in dichloromethane (0.3 mL) at 25 °C. After 24 h, imidazole (2.4 mg, 35 µmol, 1.1 equiv) and *tert*-butyldimethylchlorosilane (9.5 mg, 63 µmol, 2.0 equiv) were added. After a total of 60 h, the solution was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **47** (9.7 mg, 63%) as a colorless oil.

TLC (17% ethyl acetate in hexanes): R_f = 0.65 (UV, CAM).

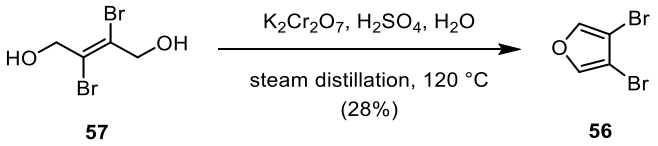
^{1}H NMR (800 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H, PMB), 6.92–6.88 (m, 2H, PMB), 6.57–6.55 (m, 1H, H-12), 5.25 (d, $^3J_{13/12}$ = 3.5 Hz, 1H, H-13), 4.75 (d, ^2J = 11.4 Hz, 1H, PMB), 4.57 (d, ^2J = 11.4 Hz, 1H, PMB), 4.44 (d, $^2J_{1a/1b}$ = 16.9 Hz, 1H, H-1a), 4.16 (dd, $^3J_{8/9}$ = 6.2, 5.1 Hz, 1H, H-8), 4.08 (d, $^2J_{1b/1a}$ = 16.9 Hz, 1H, H-1b), 3.81 (s, 3H, PMB), 2.45–2.38 (m, 1H, H-9a), 2.22–2.11 (m, 4H, H-9b, H-4, H-10a), 1.86–1.78 (m, 1H, H-10b), 1.52–1.42 (m, 2H, H-5), 0.98 (s, 3H, H-7), 0.88 (s, 9H, TBS), 0.09 (s, 3H, TBS), 0.08 (s, 3H, TBS). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 220.7 (C-11), 194.9 (C-2), 159.7 (PMB), 139.0 (C-12), 138.9 (C-3), 130.1 (PMB), 129.2 (PMB), 114.1 (PMB), 93.0 (C-13), 76.0 (C-8), 70.4 (PMB), 66.4 (C-1), 55.5 (PMB), 53.6 (C-6), 34.9 (C-9), 33.2 (C-5), 28.6 (C-10), 25.9 (TBS), 22.8 (C-4), 18.1 (TBS), 15.6 (C-7), −4.1 (TBS), −4.8 (TBS).

HR-MS (ESI): calcd for $(C_{19}H_{31}O_4Si)^+$ $(M–C_8H_9O_2)^+$: 351.1992, found: 351.1993.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930, 1738, 1692, 1612, 1515, 1464, 1250, 1161, 1115, 1033 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{21}$ = –26.9 (c = 0.09 · 10 g · mL^{-1}, CH_2Cl_2).

9.2.2 Experimental Procedures for Chapter 3.2

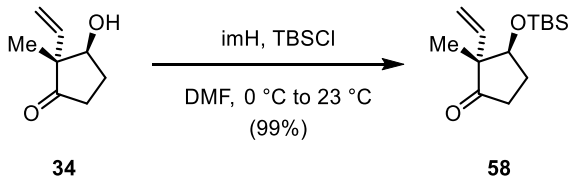


57 **56**

3,4-Dibromofuran (56).[53] 2,3-Dibromo-2-butene-1,4-diol (**57**) (19.7 g, 80.0 mmol, 1 equiv) was suspended in 7.5 wt% aqueous sulfuric acid (50 mL) and the solution was heated to 85 °C. The suspension turned clear at temperatures above 80 °C. The solution was then heated to reflux (oil bath: 120–125 °C) while a solution of potassium dichromate (24.7 g, 84.0 mmol, 1.05 equiv) in concentrated sulfuric acid (17 mL) and water (80 mL) was added dropwise via a dropping funnel while hot water steam was bubbled through the dark green solution. Within the first 1.5 h, the majority of the product has been collected. After a total of 2.5 h, the solution was cooled to 23 °C. The distillate was extracted with hexanes (3×250 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution

was filtered and the filtrate was concentrated (Caution! The product is volatile. Vacuum >200 mbar) to afford **56** (5.0 g, 28%) as a yellowish oil. The analytical data matched those previously described in the literature.[161]

Figure 10. Setup for the synthesis of 3,4-dibromofuran (**56**).



34 **58**

TBS ether 58. To a solution of ketone **34** (209 mg, 1.49 mmol, 1 equiv) in dimethylformamide (3.8 mL) were added imidazole (152 mg, 2.24 mmol, 1.50 equiv) and *tert*-butyldimethylchlorosilane (449 mg, 2.98 mmol, 2.00 equiv) at 0 °C. Upon completion of the addition, the solution was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (80 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a yellowish oil. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **58** (375 mg, 99%) as a colorless oil.

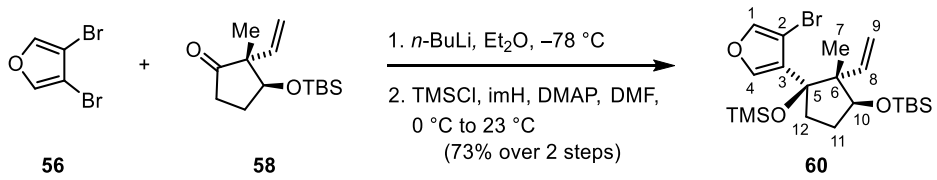
TLC (20% ethyl acetate in hexanes): R_f = 0.70 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.16–5.01 (m, 2H), 4.17 (dd, *J* = 4.5, 3.6 Hz, 1H), 2.49–2.34 (m, 1H), 2.28–2.07 (m, 2H), 1.93–1.80 (m, 1H), 1.10 (s, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 8.5 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 218.7, 138.9, 116.0, 77.6, 58.3, 34.4, 28.7, 25.9, 18.2, 16.3, −4.7, −4.7.

HR-MS (EI): calcd for $(C_{14}H_{26}O_2Si)^+$: 254.1702, found: 254.1690.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2930, 1743, 1631, 1472, 1463, 1253, 1121, 1077 cm^{-1}.

$[\alpha]_{589}^{21}$ = +38.3 (c = 0.91 · 10 g · mL^{-1}, CH_2Cl_2).

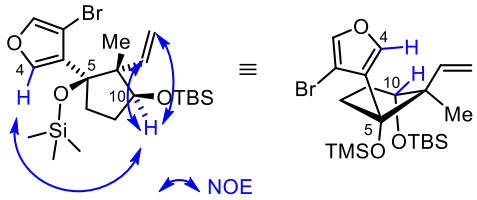


56 **58** **60**

3-Bromofuran 60. *n*-Butyllithium (2.1 M solution in hexanes, 2.06 mL, 4.33 mmol, 1.15 equiv) was added dropwise to a solution of 3,4-dibromofuran (**56**) (1.09 g, 4.33 mmol, 1.15 equiv, 90% purity) in diethyl ether (18 mL) at –78 °C. After 20 min, a solution of TBS ether **58** (958 mg,

3.77 mmol, 1 equiv) in diethyl ether (5 mL) was added dropwise. After 3 h, the solution was diluted with water (25 mL) and diethyl ether (15 mL) and the biphasic mixture was allowed to warm to 23 °C. The layers were separated and the aqueous layer was extracted with diethyl ether (3×75 mL). The combined organic layers were washed with brine (25 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow oil which was used without further purification for the next step.

The crude product (assumed 1.51 g, 3.77 mmol) was dissolved in dimethylformamide (4.2 mL) and imidazole (770 mg, 11.3 mmol, 3.00 equiv) and 4-dimethylaminopyridine (46 mg, 0.38 mmol, 0.10 equiv) were added. The solution was cooled to 0 °C. Chlorotrimethylsilane (0.96 mL, 7.54 mmol, 2.00 equiv) was added dropwise and upon completion of the addition, the solution was allowed to warm to 23 °C. After 30 min, the solution was diluted with saturated aqueous sodium bicarbonate solution (25 mL) and ethyl acetate (25 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford yellow oil. Purification by flash column chromatography on silica gel (hexanes) afforded **60** (1.31 g, 73%) as a colorless oil.



The relative stereochemistry at C-5 was established by key NOE correlations as depicted aside.

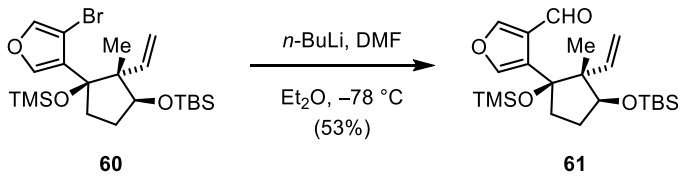
TLC (hexanes): R_f = 0.49 (UV, CAM).

^{1}H NMR (800 MHz, $CDCl_3$) δ 7.33 (d, $^3J_{1/4}$ = 1.9 Hz, 1H, H-1), 7.15 (d, $^3J_{4/1}$ = 1.9 Hz, 1H, H-4), 5.57 (dd, $^3J_{8/9}$ = 17.3, 11.1 Hz, 1H, H-8), 4.94–4.89 (m, 2H, H-9), 3.96 (dd, $^3J_{10/11a}$ = 8.1 Hz, $^3J_{10/11b}$ = 6.9 Hz, 1H, H-10), 2.25–2.17 (m, 2H, H-12), 2.12 (m, 1H, H-11a), 1.82 (m, 1H, H-11b), 1.13 (s, 3H, H-7), 0.87 (s, 9H, TBS), 0.04 (s, 9H, TMS), -0.00 (s, 3H, TBS), -0.03 (s, 3H, TBS). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 143.5 (C-8), 142.3 (C-1), 140.8 (C-4), 129.9 (C-3), 113.5 (C-9), 101.0 (C-2), 83.3 (C-5), 77.0 (C-10), 56.7 (C-6), 36.0 (C-12), 31.7 (C-11), 26.0 (TBS), 18.2 (TBS), 14.2 (C-7), 2.0 (TMS), −4.2 (TBS), −4.6 (TBS).

HR-MS (EI): calcd for $(C_{21}H_{37}BrO_3Si_2)^+$: 472.1465, found: 472.1459.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2857, 1472, 1250, 1080, 1060, 909 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +17.9 (c = 1.1 · 10 g · mL^{-1}, CH_2Cl_2).



60 **61**

Aldehyde 61. *n*-Butyllithium (2.1 M solution in hexanes, 0.50 mL, 1.1 mmol, 1 equiv) was added dropwise to a solution of 3-bromofuran **60** (500 mg, 1.06 mmol, 1 equiv) in diethyl ether (5.3 mL) at –78 °C. After 5 min, dimethylformamide (0.33 mL, 4.2 mmol, 4.0 equiv) was added. After 3 h, the solution was diluted with water (20 mL) and diethyl ether (25 mL) and the biphasic mixture was allowed to warm to 23 °C. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (40 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford **61** (238 mg, 53%) as a colorless oil.

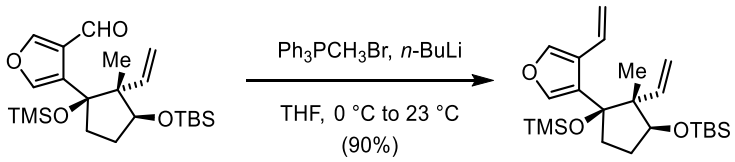
TLC (5% ethyl acetate in hexanes): R_f = 0.58 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 5.41 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.11–5.02 (m, 2H), 3.88 (t, *J* = 7.8 Hz, 1H), 2.43–2.32 (m, 1H), 2.19–2.06 (m, 2H), 1.92–1.78 (m, 1H), 1.13 (s, 3H), 0.83 (s, 9H), 0.01 (s, 9H), -0.04 (s, 3H), -0.09 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.2, 147.7, 143.4, 139.5, 131.4, 127.9, 116.6, 83.4, 76.7, 55.5, 36.9, 30.9, 25.9, 18.1, 12.9, 2.0, −4.3, −4.6.

HR-MS (ESI): calcd for $(C_{22}H_{38}O_4Si_2Na)^+$ $(M+Na)^+$: 445.2206, found: 445.2204.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956, 1683, 1569, 1528, 1472, 1252, 1089, 1058 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +7.1 (c = 0.6 · 10 g · mL^{-1}, CH_2Cl_2).



61 **63**

Diene 63. A solution of methyltriphenylphosphonium bromide (993 mg, 2.78 mmol, 1.25 equiv) in tetrahydrofuran was cooled to 0 °C and a solution of *n*-butyl lithium (2.1 M in hexanes, 1.16 mL, 2.45 mmol, 1.10 equiv) was added dropwise. After 30 min, a solution of aldehyde **61** (940 mg, 2.22 mmol, 1 equiv) in tetrahydrofuran (4.4 mL) was added dropwise. After 2 h, the suspension was diluted with water (30 mL) and diethyl ether (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×30 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (hexanes) to afford **63** (449 mg, 90%) as a colorless oil.

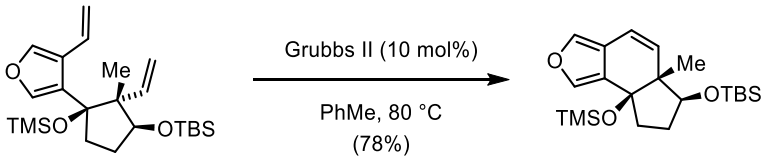
TLC (hexanes): R_f = 0.70 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.33–7.31 (m, 1H), 7.00–6.90 (m, 2H), 5.69 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.27 (dd, *J* = 17.9, 1.8 Hz, 1H), 5.12 (dd, *J* = 17.4, 1.6 Hz, 1H), 5.07–4.95 (m, 2H), 3.97 (t, *J* = 7.6 Hz, 1H), 2.21–2.11 (m, 1H), 1.94–1.68 (m, 3H), 1.32 (s, 3H), 0.97 (s, 9H), 0.09 (s, 9H), -0.00 (s, 3H), -0.04 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6) δ 144.1, 140.0, 139.6, 130.7, 130.4, 126.2, 114.9, 112.5, 84.0, 77.2, 56.0, 37.4, 31.5, 26.1, 18.3, 13.5, 2.0, −4.3, −4.5.

HR-MS (EI): calcd for $(C_{23}H_{40}O_3Si_2)^+$: 420.2516, found: 420.2512.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2857, 1629, 1472, 1250, 1091, 1066 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +15.4 (c = 0.14 · 10 g · mL^{-1}, CH_2Cl_2).



63 **64**

Tricycle 64. In a pressure flask, diene **63** (441 mg, 1.05 mmol, 1 equiv) was dissolved in freshly degassed (freeze-pump-thaw, 3 cycles) toluene (53 mL) and grubbs second generation catalyst

(89 mg, 0.11 mmol, 0.10 equiv) was added. The flask was sealed and the solution was heated to 80 °C. After 22 h, heating was ceased and the solution was allowed to cool to 23 °C. The solution was concentrated and the residue was purified by flash column chromatography on silica gel (hexanes) to afford **64** (321 mg, 78%) as a colorless oil. Some diene **63** could also be recovered (68 mg, 15%).

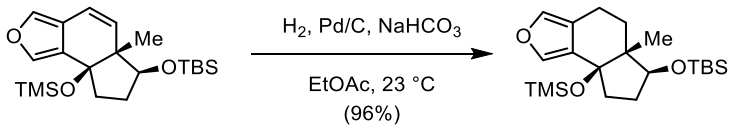
TLC (hexanes): R_f = 0.53 (UV, CAM).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.39 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.31 (d, *J* = 1.4 Hz, 1H), 6.37 (dd, *J* = 9.7, 0.8 Hz, 1H), 5.62 (d, *J* = 9.7 Hz, 1H), 3.77–3.68 (m, 1H), 2.26–2.17 (m, 2H), 1.88–1.75 (m, 1H), 1.62 (dddd, *J* = 13.3, 10.8, 8.0, 6.8 Hz, 1H), 1.10 (s, 3H), 0.85 (s, 9H), -0.07 (s, 3H), -0.09 (s, 3H), -0.12 (s, 9H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 140.1, 138.1, 137.5, 126.8, 121.9, 115.5, 79.5, 76.4, 52.7, 36.8, 30.5, 26.1, 18.5, 14.3, 1.8, −4.4, −4.6.

HR-MS (EI): calcd for $(C_{21}H_{36}O_3Si_2)^+$: 392.2203, found: 392.2196.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956, 2858, 2360, 1549, 1472, 1250, 1104, 1082 cm^{-1}.

$[\alpha]_{589}^{20}$ = +22.9 (c = 0.35 · 10 g · mL^{-1}, CH_2Cl_2).



64 **65**

Tricycle 65. To a solution of tricycle **64** (321 mg, 0.82 mmol, 1 equiv) was added sodium bicarbonate (442 mg, 5.26 mmol, 6.40 equiv), followed by palladium on charcoal (87 mg, 82 μmol, 0.10 equiv). An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 1 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 18 h, hydrogen gas was released from the flask and the suspension was filtered through a short pad of celite. The filter cake was rinsed with ethyl acetate and the filtrate was concentrated to afford **65** (311 mg, 96%) as a colorless oil.

TLC (hexanes): R_f = 0.62 (UV, CAM).

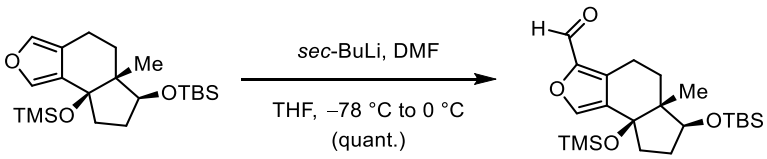
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.39 (d, *J* = 1.5 Hz, 1H), 7.12 (q, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 8.8, 7.3 Hz, 1H), 2.65–2.56 (m, 1H), 2.45 (dddd, *J* = 16.8, 11.9, 6.9, 1.8 Hz, 1H), 2.26–2.13 (m, 1H),

2.07–1.98 (m, 1H), 1.79 (app dtd, *J* = 13.2, 9.2, 6.5 Hz, 1H), 1.68–1.48 (m, 3H), 0.91 (s, 3H), 0.88 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H), -0.06 (s, 9H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 140.5, 137.7, 129.5, 121.0, 76.3, 72.5, 48.8, 37.3, 30.3, 27.2, 26.1, 18.4, 16.3, 16.0, 2.1, −4.0, −4.7.

HR-MS (EI): calcd for $(C_{21}H_{38}O_3Si_2)^+$: 394.2359, found: 394.2353.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2929, 2895, 2857, 1535, 1471, 1463, 1362, 1299, 1249, 1135, 1102, 1083, 1057, 1047 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +4.2 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



65 **66**

Aldehyde 66. *sec*-Butyllithium (1.1 M in cyclohexane, 0.79 mL, 0.86 mmol, 1.1 equiv) was added to a solution of tricycle **65** (311 mg, 0.790 mmol, 1 equiv) in tetrahydrofuran (3.9 mL) at –78 °C. After 45 min, dimethylformamide (0.24 mL, 3.1 mmol, 4.0 equiv) was added. After 30 min, the solution was allowed to warm to –30 °C. After further 30 min, the solution was allowed to warm to 0 °C. After 1 h, the solution was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford **66** (333 mg, quant., 10:1 mixture of regioisomers) as a colorless oil.

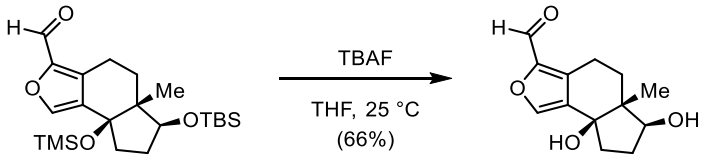
TLC (10% ethyl acetate in hexanes): R_f = 0.37 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.60 (s, 1H), 3.72 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.01 (ddd, *J* = 18.8, 6.1, 2.7 Hz, 1H), 2.67 (ddd, *J* = 18.8, 11.2, 7.7 Hz, 1H), 2.31–2.20 (m, 1H), 2.08–1.96 (m, 1H), 1.83–1.71 (m, 1H), 1.71–1.58 (m, 3H), 0.93 (s, 3H), 0.88 (s, 9H), −0.01 (s, 3H), −0.02 (s, 9H), −0.04 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.8, 147.3, 145.2, 142.6, 132.4, 75.5, 71.8, 48.4, 36.5, 29.9, 26.0, 25.9, 18.1, 17.1, 15.9, 2.2, −4.0, −4.7.

HR-MS (ESI): calcd for $(C_{22}H_{39}O_4Si_2)^+$ $(M+H)^+$: 423.2387, found: 423.2387.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2857, 1682, 1595, 1519, 1472, 1370, 1251, 1107, 1087 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +6.8 (c = 0.73 · 10 g · mL^{-1}, CH_2Cl_2).



66 **67**

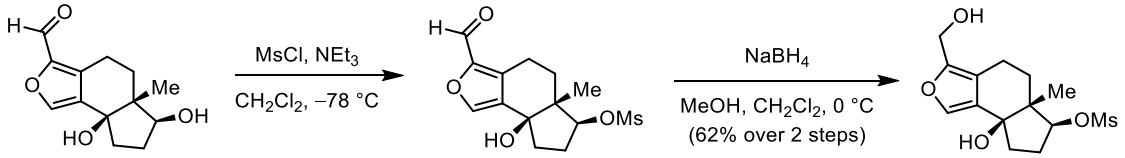
Diol 67. Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 1.43 mL, 1.10 equiv) was added dropwise to a solution of aldehyde **66** (550 mg, 1.30 mmol, 1 equiv) in tetrahydrofuran (6.5 mL) at 25 °C. After 1.5 h, the solution was diluted with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (66% ethyl acetate in hexanes) to afford **67** (204 mg, 66%) as a white solid.

TLC (66% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.68 (s, 1H), 7.66 (s, 1H), 3.92 (td, *J* = 6.1, 1.4 Hz, 1H), 3.06–2.74 (m, 3H), 2.36–2.17 (m, 3H), 2.06 (ddd, *J* = 15.2, 11.5, 6.0 Hz, 1H), 1.94–1.80 (m, 1H), 1.69–1.46 (m, 2H), 1.06 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 178.5, 147.8, 144.7, 132.1, 81.5, 80.2, 49.6, 40.6, 32.2, 31.7, 17.7, 12.6. (one aryl carbon is missing).

HR-MS (EI): calcd for $(C_{13}H_{16}O_4)^+$: 236.1049, found: 236.1034.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3406, 2938, 2852, 2022, 1666, 1598, 1416, 1371 cm^{-1}.



67 54 69

Mesylate 54. To a solution of diol **67** (54 mg, 0.23 mmol, 1 equiv) in dichloromethane (4 mL) was added triethylamine (73 µL, 0.53 mmol, 2.3 equiv) and the solution was cooled to –78 °C. After 3.5 h, the solution was diluted with saturated aqueous sodium chloride solution (10 mL) and dichloromethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×25 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford **54** as a yellow solid. The crude product was used without further purification for the next step.

TLC (66% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.73 (s, 1H), 4.78 (dd, *J* = 7.5, 3.9 Hz, 1H), 3.02 (s, 3H), 2.99–2.83 (m, 2H), 2.41–2.25 (m, 2H), 2.23–2.04 (m, 2H), 2.03 (s, 1H), 1.82–1.63 (m, 2H), 1.10 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.6, 147.8, 145.4, 131.7, 88.0, 77.8, 49.3, 39.2, 38.9, 31.4, 29.8, 17.5, 14.0.

HR-MS (EI): calcd for $(C_{14}H_{18}O_6S)^+$: 314.0824, found: 314.0838.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3432, 1669, 1597, 1347, 1172, 936 cm^{-1}.

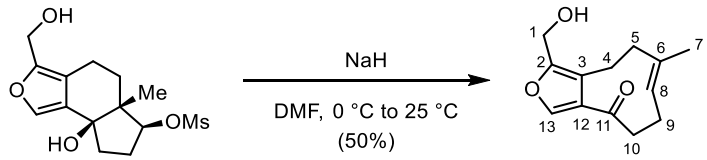
Crude **54** (assumed 72 mg, 0.23 mmol, 1 equiv) was dissolved in a mixture of methanol and dichloromethane (v/v = 1:1, 2.5 mL) and the solution was cooled to 0 °C. Sodium borohydride (9.5 mg, 0.25 mmol, 1.1 equiv) was added. After 10 min, the solution was diluted with pH 7 phosphate buffer solution (10 mL) and dichloromethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford a yellow oil. The crude product was purified by flash column chromatography on silica gel (66% ethyl acetate in hexanes) to afford **69** (45 mg, 62% over 2 steps) as a colorless oil.

TLC (100% ethyl acetate in hexanes): R_f = 0.47 (CAM).

^{1}H NMR (800 MHz, CD_2Cl_2) δ 7.46 (s, 1H), 4.77 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.51 (d, *J* = 4.5 Hz, 2H), 3.00 (s, 3H), 2.63–2.58 (m, 2H), 2.31–2.22 (m, 2H), 2.13–2.02 (m, 2H), 1.86 (s, 1H), 1.74–1.61 (m, 3H), 1.08 (s, 3H). **^{13}C NMR** (200 MHz, CD_2Cl_2) δ 148.5, 139.4, 129.9, 117.3, 87.4, 77.7, 56.2, 49.0, 38.9, 38.9, 31.6, 29.5, 16.2, 14.3.

HR-MS (EI): calcd for $(C_{14}H_{20}O_6S)^+$: 316.0981, found: 316.0977.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3396, 2938, 1557, 1344, 1171 cm^{-1}.



69 **53**

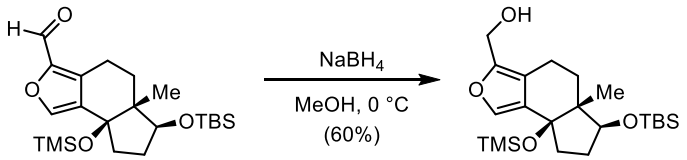
Cyclononene 53. Sodium hydride (11.4 mg, 0.280 mmol, 2.00 equiv, 60% dispersion in mineral oil) was added in two portions within 15 min to a solution of mesylate **69** (45 mg, 0.14 mmol, 1 equiv) in dimethylformamide (1.2 mL) at 0 °C. After 15 min, the solution was allowed to warm to 25 °C. After 2 h, the solution was carefully diluted with pH 7 buffer solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow oil. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **53** (16 mg, 50%) as a colorless oil.

TLC (50% ethyl acetate in hexanes): R_f = 0.54 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H, H-13), 5.08 (ddd, $^3J_{8/9}$ = 12.2 Hz, ^3J = 4.5, 1.7 Hz, 1H, H-8), 4.58 (s, 2H, H-1), 3.01 (td, $^3J_{10/9}$ = 10.4, 8.4 Hz, 1H, H-10a), 2.77 (tdd, $^3J_{9a/8}$ = 12.2 Hz, $^3J_{9a/10}$ = 10.6, 8.1 Hz, 1H, H-9a), 2.68–2.57 (m, 2H, H-10b, H-4a), 2.46 (ddd, $^3J_{4/5}$ = 14.1, 12.8 Hz, $^2J_{4a/4b}$ = 2.4 Hz, 1H, H-4b), 2.35–2.20 (m, 2H, H-9b, H-5a), 1.78 (m, 2H, H-5b, OH), 1.62 (s, 3H, H-7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.9 (C-11), 150.2 (C-2), 139.7 (C-13), 135.8 (C-6), 133.4 (C-12), 125.0 (C-8), 120.9 (C-3), 55.3 (C-2), 44.4 (C-10), 41.4 (C-5), 24.3 (C-9), 21.5 (C-4), 16.8 (C-7).

HR-MS (EI): calcd for $(C_{13}H_{16}O_3)^+$: 220.1099, found: 220.1093.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3413, 2926, 2854, 1688, 1537, 1453 cm^{-1}.



66 **75**

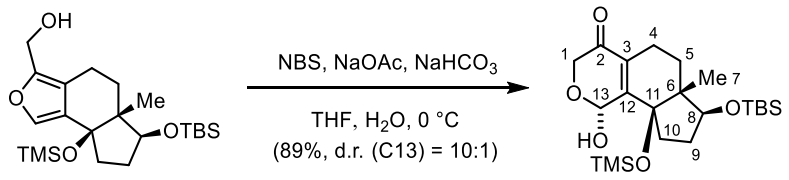
Furfuryl alcohol 75. Sodium borohydride (16 mg, 0.43 mmol, 1.1 equiv) was added to a solution of aldehyde **66** (166 mg, 0.390 mmol, 1 equiv) in methanol (3.9 mL) at 0 °C. After 30 min, saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a yellowish oil. The crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **75** (100 mg, 60%) as colorless oil.

TLC (15% ethyl acetate in hexanes): R_f = 0.27 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 4.54 (d, *J* = 2.2 Hz, 2H), 3.77 (dd, *J* = 8.7, 7.3 Hz, 1H), 2.58 (ddd, *J* = 16.7, 6.5, 2.5 Hz, 1H), 2.40 (ddd, *J* = 16.8, 11.7, 7.0 Hz, 1H), 2.19 (td, *J* = 12.5, 6.4 Hz, 1H), 1.99 (ddd, *J* = 12.6, 9.4, 4.3 Hz, 1H), 1.84–1.69 (m, 2H), 1.68–1.50 (m, 3H), 0.90 (s, 3H), 0.87 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H), -0.06 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.3, 139.4, 123.0, 118.3, 75.9, 72.1, 56.0, 48.4, 36.9, 30.0, 26.8, 25.9, 18.1, 16.1, 15.7, 2.1, −4.0, −4.7.

HR-MS (EI): calcd for $(C_{22}H_{40}O_4Si_2)^+$: 424.2465, found: 424.2464.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3319, 2954, 2857, 1471, 1462, 1249 cm^{-1}.



75 **76**

Lactol 76. To a solution of furfuryl alcohol **75** (38 mg, 89 μmol, 1 equiv) in a mixture of tetrahydrofuran/ water (v/v = 4:1, 0.9 mL) were added sodium bicarbonate (15 mg, 0.18 mmol, 2.0 equiv) and sodium acetate (7.3 mg, 89 μmol, 1 equiv), successively. The solution was cooled to 0 °C and *N*-bromosuccinimide (16 mg, 89 μmol, 1 equiv) was added. After 30 min, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford **76** (38 mg, 89%, d.r. = 7:1) as a crystalline off-white solid. Recrystallization of the product from diethyl ether gave crystals suitable for single crystal X-ray diffraction analysis.

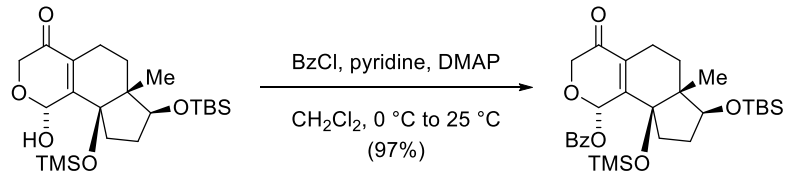
TLC (20% ethyl acetate in hexanes): R_f = 0.33 (UV, CAM).

Peaks of the minor diastereomer are also visible in the NMR spectra, but only chemical shifts of the major diastereomer are reported:

^{1}H NMR (800 MHz, C_6D_6) δ 5.52 (d, $^3J_{13/OH}$ = 3.7 Hz, 1H, H-13), 4.49 (d, $^2J_{1a/1b}$ = 17.4 Hz, 1H, H-1a), 4.02 (d, $^2J_{1b/1a}$ = 17.4 Hz, 1H, H-1b), 3.78 (dd, *J* = 8.7, 6.7 Hz, 1H, H-8), 2.45–2.31 (m, 2H, H-4), 2.14 (ddd, *J* = 13.8, 9.3, 4.9 Hz, 1H, H-10a), 2.02 (ddd, *J* = 13.3, 11.7, 6.5 Hz, 1H, H-10b), 1.92 (d, $^3J_{OH/13}$ = 4.3 Hz, 1H, OH), 1.90–1.83 (m, 1H, H-9a), 1.62–1.54 (m, 1H, H-9b), 1.49 (ddd, *J* = 14.0, 6.5, 3.2 Hz, 1H, H-5a), 1.41 (ddd, *J* = 14.0, 10.4, 6.7 Hz, 1H, H-5b), 1.05 (s, 3H, H-7), 0.94 (s, 9H, TBS), 0.19 (s, 9H, TMS), -0.07 (s, 3H, TBS), -0.08 (s, 3H, TBS). **^{13}C NMR** (200 MHz, C_6D_6) δ 195.0 (C-2), 152.5 (C-12), 130.8 (C-3), 88.9 (C-13), 81.1 (C-11), 73.3 (C-8), 65.2 (C-1), 47.8 (6), 33.1 (C-10), 30.2 (C-9), 26.5 (C-5), 26.1 (TBS), 18.3 (C-4), 18.2 (TBS), 17.5 (C-7), 2.8 (TMS), −4.3 (TBS), −4.9 (TBS).

HR-MS (EI): calcd for $(C_{22}H_{40}O_5Si_2)^+$: 440.2414, found: 440.2404.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3406, 2955, 2929, 1687, 1672, 1251, 1087 cm^{-1}.



76 **77d**

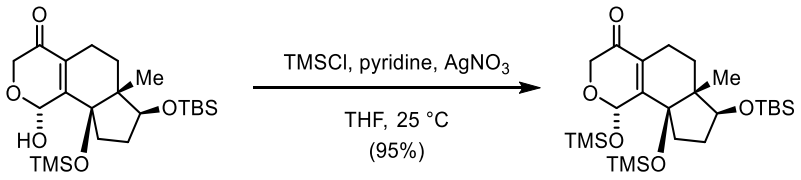
Benzoat 77d. To a solution of lactol **76** (47 mg, 0.11 mmol, 1 equiv) in dichloromethane (10 mL) were added pyridine (17 μL, 0.21 mmol, 2.0 equiv) and 4-dimethylaminopyridine (1.3 mg, 11 μmol, 0.10 equiv) and the solution was cooled to 0 °C. Benzoyl chloride (15 μL, 0.13 mmol, 1.2 equiv) was added dropwise and upon completion of the addition the solution was allowed to warm to 25 °C. After 14 h, the solution was diluted with saturated aqueous sodium chloride solution (10 mL) and dichloromethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford a yellow oil. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **77d** (56 mg, 97%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.34 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.44–7.38 (m, 1H), 7.30–7.23 (m, 2H), 6.71 (s, 1H), 4.31 (d, *J* = 17.8 Hz, 1H), 4.03 (d, *J* = 17.8 Hz, 1H), 3.59 (dd, *J* = 8.1, 6.5 Hz, 1H), 2.13 (tt, *J* = 5.9, 2.4 Hz, 2H), 1.86–1.75 (m, 1H), 1.61–1.48 (m, 2H), 1.43–1.25 (m, 3H), 0.72 (s, 3H), 0.67 (s, 9H), 0.00 (s, 9H), -0.17 (s, 3H), -0.21 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.4, 165.2, 150.4, 134.0, 132.6, 130.0, 129.2, 128.9, 88.0, 81.0, 73.4, 66.4, 47.9, 32.7, 30.5, 26.8, 25.9, 18.2, 18.1, 17.3, 2.9, −4.2, −4.7.

HR-MS (EI): calcd for $(C_{29}H_{44}O_6Si_2)^+$: 544.2676, found: 544.2669.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2928, 1791, 1731, 1689, 1471, 1252, 1080 cm^{-1}.



76 **77f**

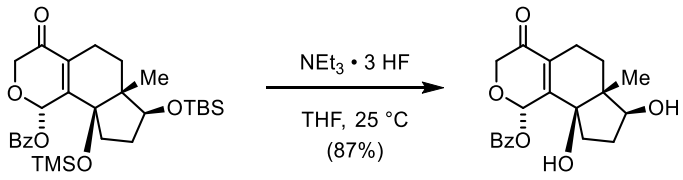
TMS acetal 77f. To a solution of lactol **76** (9.7 mg, 22 μmol, 1 equiv) in tetrahydrofuran (0.25 mL) were added pyridine (8.0 μL, 99 μmol, 4.5 equiv) and silver(I) nitrate (4.5 mg, 26 μmol, 1.2 equiv). The suspension was stirred at 25 °C. After 10 min, chlorotrimethylsilane (3.7 μL, 29 μmol, 1.3 equiv) was added and a thick white precipitate was formed. After 5 min, the suspension was filtered through a short pad of silica gel and the filter cake was rinsed with ethyl acetate (10 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford **77f** (10.7 mg, 95%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.77 (UV, CAM).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.61 (d, *J* = 1.1 Hz, 1H), 4.44 (d, *J* = 17.5 Hz, 1H), 4.02 (d, *J* = 17.5 Hz, 1H), 3.74 (dd, *J* = 8.9, 6.6 Hz, 1H), 2.27–2.08 (m, 2H), 2.10–1.94 (m, 2H), 1.79 (dtd, *J* = 13.2, 9.0, 7.1 Hz, 1H), 1.59–1.49 (m, 2H), 1.49–1.37 (s, 1H), 0.90 (s, 3H), 0.88 (s, 9H), 0.22 (s, 9H), 0.15 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 196.6, 154.0, 130.0, 89.4, 81.1, 72.8, 65.5, 47.8, 32.6, 30.1, 26.2, 26.1, 18.4, 18.2, 17.8, 3.0, 0.1, −4.1, −4.6.

HR-MS (EI): calcd for $(C_{25}H_{48}O_5Si_3)^+$: 512.2810, found: 512.2813.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956, 2929, 1689, 1472, 1251, 1089 cm^{-1}.



77d **80**

Diol 80. Benzoate **77d** (21 mg, 39 μmol, 1 equiv) was dissolved in tetrahydrofuran (0.5 mL) and triethylamine trihydrofluoride (63 μL, 0.39 mmol, 10 equiv) was added. After 14 h, the solution was diluted with half-saturated sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The

combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **80** (12 mg, 87%) as a colorless oil.

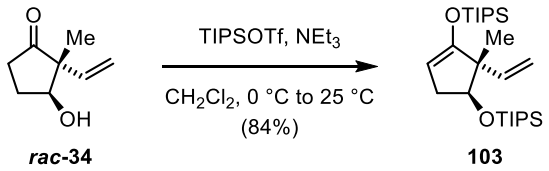
TLC (33% ethyl acetate in hexanes): R_f = 0.16 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 8.13–8.07 (m, 2H), 7.68 (d, *J* = 1.9 Hz, 1H), 7.15–7.09 (m, 1H), 7.08–7.01 (m, 2H), 4.36 (d, *J* = 16.9 Hz, 1H), 4.06 (d, *J* = 16.9 Hz, 1H), 3.23 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.18 (s, 1H), 2.53 (ddd, *J* = 19.0, 6.4, 1.8 Hz, 1H), 2.02 (dddd, *J* = 18.7, 12.0, 6.5, 2.1 Hz, 1H), 1.91 (ddd, *J* = 14.2, 10.1, 4.5 Hz, 1H), 1.74 (ddd, *J* = 14.0, 11.7, 5.2 Hz, 1H), 1.63 (dddd, *J* = 14.6, 11.7, 5.6, 4.4 Hz, 1H), 1.38–1.26 (m, 2H), 0.90 (ddd, *J* = 13.8, 6.5, 1.8 Hz, 1H), 0.85–0.73 (m, 4H). **^{13}C NMR** (100 MHz, C_6D_6) δ 193.4, 164.9, 151.5, 133.5, 130.4, 130.2, 130.0, 128.8, 87.4, 81.6, 81.3, 66.3, 49.0, 40.4, 31.5, 29.1, 18.3, 12.7.

HR-MS (EI): calcd for $(C_{20}H_{22}O_6)^+$: 358.1416, found: 358.1413.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3468, 2939, 2279, 1729, 1685, 1451, 1266, 1082, 1064 cm^{-1}.

9.2.3 Experimental Procedures for Chapter 3.3



***rac*-34** **103**

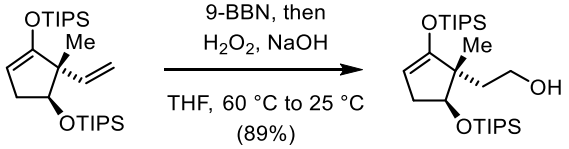
TIPS enol ether 103. Alcohol ***rac*-34** (4.99 g, 35.6 mmol, 1 equiv) was dissolved in dichloromethane (178 mL) and the solution was cooled to 0 °C. Triethylamine (20.8 mL, 150 mmol, 4.20 equiv) was added, followed by triisopropylsilyl trifluoromethanesulfonate (19.6 g, 73.0 mmol, 2.05 equiv). The solution was allowed to warm to 25 °C and after 30 min, saturated aqueous ammonium chloride solution (60 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography (hexanes) to afford **103** (13.5 g, 84%) as a colorless oil.

TLC (hexanes): R_f = 0.76 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.12–4.98 (m, 2H), 4.35 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.24 (t, *J* = 6.9 Hz, 1H), 2.46 (ddd, *J* = 14.1, 7.1, 2.8 Hz, 1H), 2.19–2.08 (m, 1H), 1.22–1.13 (m, 3H), 1.12 (s, 3H), 1.08–1.02 (m, 39H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.4, 144.4, 113.5, 95.3, 78.5, 54.0, 36.4, 18.3, 18.2, 18.2, 18.2, 15.3, 12.7, 12.6.

HR-MS (EI): calcd for $(C_{26}H_{51}O_2Si_2)^+$ $(M–H)^+$: 451.3428, found: 451.3411.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2867, 1642, 1464, 1246, 1105 cm^{-1}.



103 **104**

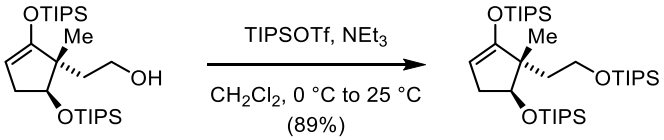
Alcohol 104. 9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 2.36 mL, 1.18 mmol, 1.15 equiv) was added dropwise to a solution of TIPS enol ether **103** (464 mg, 1.02 mmol, 1 equiv) in tetrahydrofuran (2 mL) at 25 °C. The mixture was heated to 60 °C. After 4 h, the mixture was cooled to 0 °C and aqueous sodium hydroxide solution (10 wt%, 3.07 mL, 9.22 mmol, 9.00 equiv) followed by aqueous hydrogen peroxide (30 wt%, 0.942 mL, 9.22 mmol, 9.00 equiv) were added. The solution was allowed to warm to 25 °C. After 2 h, the solution was diluted with water (20 mL) and ethyl acetate (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The colorless crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **104** (428 mg, 89%) as a colorless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.78 (CAM).

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (t, *J* = 2.4Hz, 1H), 4.22 (t, *J* = 7.2Hz, 1H), 3.72 (q, *J* = 6.1Hz, 2H), 2.53–2.28 (m, 2H), 2.24–2.08 (m, 1H), 1.85–1.61 (m, 2H), 1.09 (d, *J* = 6.1Hz, 45H).

HR-MS (EI): calcd for $(C_{26}H_{54}O_3Si_2)^+$: 470.3611, found: 470.3586.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2941, 2889,2864, 1462, 1096, 1064 cm^{-1}.



104 **S1**

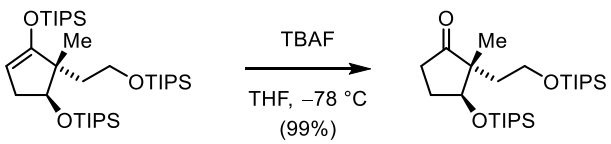
TIPS enol ether S1. Alcohol **104** (1.24 g, 2.63 mmol, 1 equiv) was dissolved in dichloromethane (13.5 mL) and the solution was cooled to 0 °C. Triethylamine (0.81 mL, 5.8 mmol, 2.2 equiv) was added followed by triisopropylsilyl trifluoromethanesulfonate (0.740 mL, 2.77 mmol, 1.05 equiv). The solution was allowed to warm to 25 °C and after 40 min, saturated aqueous ammonium chloride solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (hexanes) to afford **S1** (1.46 g, 89%) as a colorless oil.

TLC (hexanes): R_f = 0.47 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, *J* = 2.4 Hz, 1H), 4.21 (t, *J* = 6.8 Hz, 1H), 3.79–3.69 (m, 2H), 2.42 (ddd, *J* = 14.2, 7.2, 2.8 Hz, 1H), 2.09 (ddd, *J* = 14.1, 6.4, 2.0 Hz, 1H), 1.82–1.63 (m, 2H), 1.11–1.01 (m, 63H), 1.00 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 94.9, 76.5, 60.7, 49.3, 40.3, 36.2, 18.3, 18.3, 18.2, 18.2, 18.0, 12.7, 12.7, 12.2.

HR-MS (EI): calcd for $(C_{35}H_{74}O_3Si_3)^+$: 626.4946, found: 626.4937.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 2892, 1640, 1463, 1106, 1069 cm^{-1}.



S1 **105**

Ketone 105. Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 20.2 mL, 20.2 mmol, 1.02 equiv) was added dropwise to a solution of TIPS enol ether **S1** (12.4 g, 19.8 mmol, 1 equiv) in tetrahydrofuran (198 mL) at −78 °C. After 10 min, saturated aqueous sodium bicarbonate solution (160 mL) was added and the mixture was allowed to warm to 25 °C. Ethyl acetate (25 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate

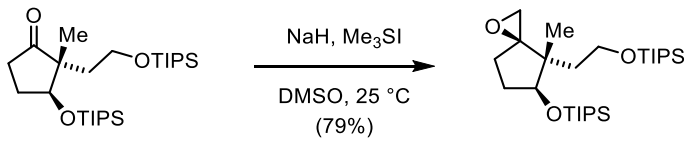
(3×50 mL), the combined layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford a colorless oil. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **105** (9.20 g, 99%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.44 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (t, *J* = 5.6 Hz, 1H), 3.78–3.70 (m, 2H), 2.47–2.30 (m, 1H), 2.29–2.16 (m, 2H), 1.93–1.82 (m, 1H), 1.77 (dt, *J* = 14.0, 7.5 Hz, 1H), 1.63 (dt, *J* = 14.0, 6.3 Hz, 1H), 1.12–0.98 (m, 45H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 76.4, 59.6, 52.9, 38.1, 34.9, 28.9, 18.3, 18.3, 18.1, 16.5, 12.7, 12.1.

HR-MS (EI): calcd for $(C_{25}H_{51}O_3Si_2)^+$ $(M–CH_3)^+$: 455.3371, found: 455.3370.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2941, 2865, 1743, 1462, 1101, 1067, 1012 cm^{-1}.



105 **106**

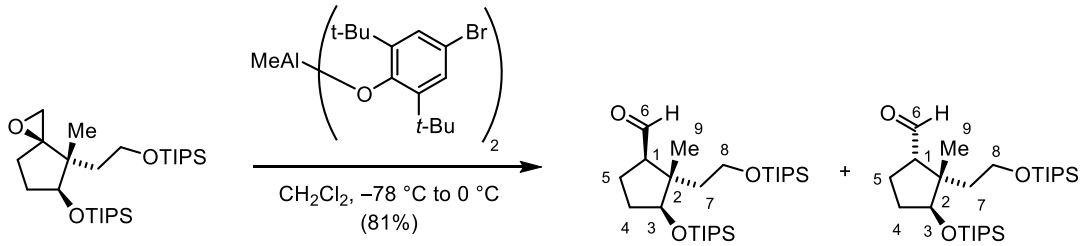
Epoxide 106. Sodium hydride (60% dispersion in mineral oil, 81.5 mg, 2.04 mmol, 1.20 equiv) was added to dimethyl sulfoxide (6.8 mL) and trimethylsulfonium iodide (416 mg, 2.04 mmol, 1.20 equiv) was added in one portion. The solution was stirred for 30 min before a solution of ketone **105** (800 mg, 1.70 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added to the yellow solution. After 18 h, the dark red solution was diluted with water (5 mL) and diethyl ether (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (6×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2×20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford an orange oil. The crude product was purified by flash column chromatography on silica gel (5% diethyl ether in pentanes) to afford **106** (654 mg, 79%) as a colorless oil.

TLC (5% diethyl ether in pentanes): R_f = 0.38 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18–4.14 (m, 1H), 3.78–3.66 (m, 2H), 2.75 (d, *J* = 4.7 Hz, 1H), 2.64 (d, *J* = 4.7 Hz, 1H), 2.05–1.72 (m, 4H), 1.66–1.42 (m, 2H), 1.13–0.99 (m, 42H), 0.87 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 79.0, 68.0, 59.9, 49.5, 45.7, 40.7, 30.9, 29.0, 18.4, 18.3, 18.2, 14.5, 12.8, 12.1.

HR-MS (EI): calcd for $(C_{26}H_{54}O_3Si_2)^-$ $(M–CH_2)^-$: 470.3611, found: 470.3413.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2941, 2865, 1462, 1101, 1065, 1012 cm^{-1}.



Carbaldehyde 107. 4-Bromo-2,6-di-*tert*-butylphenol (9.46 g, 33.2 mmol, 4.00 equiv) was dissolved in dichloromethane (44 mL) and trimethylaluminium (2 M in toluene, 8.29 mL, 16.6 mmol, 2.00 equiv) was added at 25 °C. The yellow mixture was stirred for 1 h, before it was cooled to −78 °C. A solution of epoxide **106** (4.02 g, 8.29 mmol, 1 equiv) in dichloromethane (10 mL) was added dropwise. After 1 h, the solution was allowed to warm to −40 °C. After 30 min, the mixture was allowed to warm to 0 °C. Stirring was continued for 30 min and then aqueous hydrochloric acid (1 M, 8 mL), dichloromethane (10 mL) and water (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (30 mL), followed by saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow oil and the crude product was purified by flash column chromatography on silica gel (10% to 30% dichloromethane in hexanes), to afford **107** (1.57 g, 39%) and **S2** (1.91 g, 48%) as colorless oils.

Minor diastereomer (107):

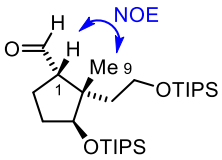
TLC (30% dichloromethane in hexanes): R_f = 0.14 (CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 9.77 (d, *J* = 2.5 Hz, 1H, H-6), 3.92–3.80 (m, 3H, H-3, H-8), 2.41 (ddd, *J* = 9.3, 7.2, 2.5 Hz, 1H, H-1), 2.09–2.00 (m, 1H, H-5a), 1.85–1.78 (m, 1H, H-7a), 1.74–1.66 (m, 2H, H-7b, H-4a), 1.55–1.44 (m, 1H, H-4b), 1.44–1.34 (m, 2H, H-5b), 1.15–1.03 (m, 42H, TIPS), 0.98 (s, 3H, H-9). **^{13}C NMR** (101 MHz, C_6D_6) δ 203.0 (C-6), 80.6 (C-3), 60.5 (C-8), 56.6 (C-1), 48.5 (C-2), 43.3 (C-7), 31.5 (C-4), 19.9 (C-5), 18.4 (TIPS), 18.4 (TIPS), 18.3 (TIPS), 15.1 (C-9), 12.9 (TIPS), 12.3 (TIPS).

HR-MS (ESI): calcd for $(C_{27}H_{57}O_3Si_2)^+$: 485.3841, found: 485.3847.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2892, 2867, 1720, 1606, 1463, 1384, 1365, 1248, 1129, 1100, 1070, 1014 cm^{-1}.

Major diastereomer (S2):



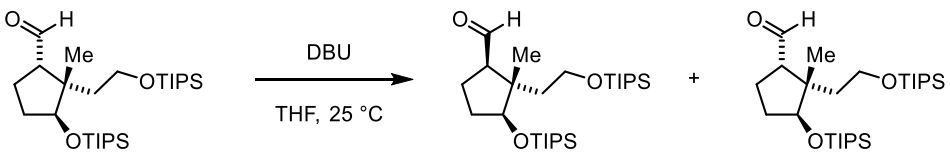
The relative stereochemistry at C-1 was established by the key NOE correlation as depicted aside.

TLC (30% dichloromethane in hexanes): R_f = 0.17 (CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 9.76 (d, *J* = 2.0 Hz, 1H), 4.18–4.15 (m, 1H, H-3), 3.76 (td, *J* = 6.5, 2.1 Hz, 2H, H-8), 2.67–2.63 (m, 1H, H-1), 2.00–1.87 (m, 2H, H-4a, H-5a), 1.68–1.60 (m, 3H, H-5b, H-7), 1.56–1.50 (m, 1H, H-4b), 1.18 (s, 3H, H-9), 1.11–1.02 (m, 42H). **^{13}C NMR** (101 MHz, C_6D_6) δ 203.6 (C-6), 80.4 (C-3), 60.5 (C-8), 58.9 (C-1), 49.6 (C-2), 38.2 (C-7), 31.7 (C-4), 20.6 (C-5), 19.8 (C-9), 18.5 (TIPS), 18.4 (TIPS), 18.3 (TIPS), 12.9 (TIPS), 12.3 (TIPS).

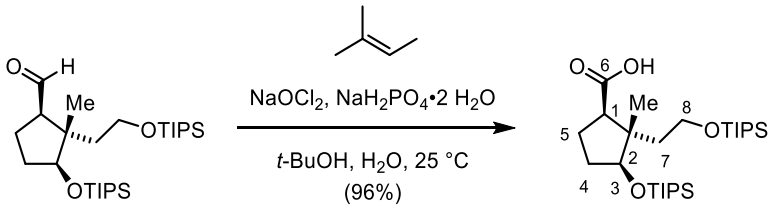
HR-MS (EI): calcd for $(C_{27}H_{56}O_3Si_2)^+$: 484.3786, found: 484.3750.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2892, 2867, 2714, 1721, 1464, 1383, 1366, 1246, 1149, 1099, 1068 cm^{-1}.



S2 **107** (65%) **S2** (34%)

Isomerization of carbaldehyde S2. Carbaldehyde **S2** (1.91 g, 3.94 mmol, 1 equiv) was dissolved in tetrahydrofuran (15 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.17 mL, 7.84 mmol, 2.00 equiv) was added at 25 °C. After 7 h, the solvent was removed and the colorless crude product was purified by flash column chromatography on silica gel (10% to 30% dichloromethane in hexanes) to afford a mixture of carbaldehyde **107** (1.23 g, 2.54 mmol, 65%) and carbaldehyde **S2** (646 mg, 1.33 mmol, 34%). Through repetition of this isomerization a total yield of carbaldehyde **107** (3.16 g, 6.55 mmol, 78%) could be obtained over two steps from epoxide **106**.



107 **108**

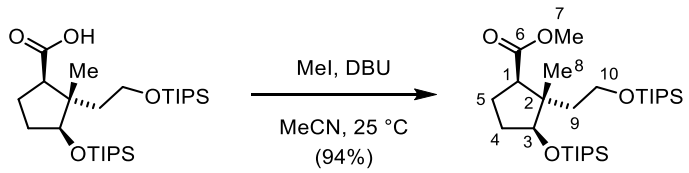
Carboxylic acid 108. 2-Methyl-2-butene (23.9 mL, 225 mmol, 40.0 equiv) was added to a solution of carbaldehyde **107** (2.73 g, 5.63 mmol, 1 equiv) in *tert*-butanol (165 mL) at 25 °C. A solution of monosodium dihydrogenphosphate dihydrate (2.63 g, 16.9 mmol, 3.00 equiv) and sodium chlorite (1.53 g, 16.9 mmol, 3.00 equiv) in water (188 mL) was added via a drop addition funnel. After 1 h, water (20 mL), diethyl ether (20 mL) and aqueous hydrochloric acid (1 M, 15 mL) were added sequentially. The mixture was stirred for 10 min before the layers were separated. The aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with aqueous saturated sodium chloride solution (20 mL) and the aqueous layer was extracted with diethyl ether (310 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to yield a colorless oil, which was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **109** (2.72 g, 96%) as a colorless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.68 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (br s, 1H, H-6), 4.02 (t, J = 8.2 Hz, 1H, H-3), 3.94−3.83 (m, 2H, H-8), 2.79 (t, $^3J_{1/5}$ = 8.6 Hz, 1H, H-1), 2.33−2.22 (m, 1H, H-5a), 2.02−1.89 (m, 2H, H-4a, H-7a), 1.80−1.64 (m, 3H, H-4b, H-5b, H-7b) 1.22−1.05 (m, 42H, TIPS), 0.88 (s, 3H, H-9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0 (C-6), 77.8 (C-3), 60.3 (C-8), 48.5 (C-1), 46.9 (C-2), 38.8 (C-7), 30.1 (C-4), 21.5 (C-5), 18.3 (TIPS), 18.2 (TIPS), 18.0 (TIPS), 18.0 (TIPS), 16.2 (C-9), 12.7 (TIPS), 11.9 (TIPS).

HR-MS (ESI): calcd for $(C_{27}H_{57}O_4Si_2)^+$ $(M+H)^+$: 501.3790, found: 501.3794.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 2890, 2866, 1704, 1463, 1419, 1384, 1365, 1293, 1240, 1127, 1102, 1068, 1013 cm^{-1}.



108 **109**

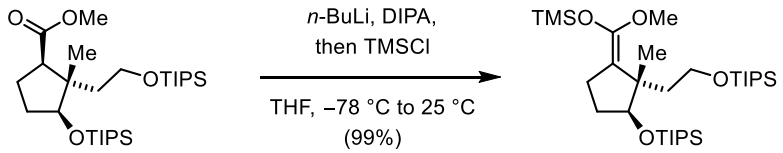
Methyl ester 109. Carboxylic acid **108** (1.46 g, 2.91 mmol, 1 equiv) was dissolved in acetonitrile (26 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.33 mL, 8.72 mmol, 3.00 equiv) and iodomethane (0.907 mL, 14.6 mmol, 5.00 equiv) were added subsequently. After 2 h, water (20 mL) and ethyl acetate (20 mL). were added to the resulting yellow solution. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a yellow oil. The crude product was purified by flash column chromatography (5% ethyl acetate in hexanes) to afford **109** (1.41 g, 94%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.46 (Anis).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (t, $^3J_{3/4}$ = 8.1 Hz, 1H, H-3), 3.90–3.73 (m, 2H, H-10), 3.66 (s, 3H, H-7), 2.61 (t, $^3J_{1/5}$ = 9.1 Hz, 1H, H-1), 2.17–2.05 (m, 1H, H-5a), 1.91–1.85 (m, 1H, H-4a), 1.82–1.78 (m, 2H, H-9), 1.71–1.62 (m, 2H, H-4b, H-5b), 1.07–1.05 (m, 42H, TIPS), 0.83 (s, 3H, H-8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0 (C-6), 79.4 (C-3), 60.2 (C-10), 51.4 (C-7), 48.9 (C-1), 47.3 (C-2), 42.0 (C-9), 30.8 (C-4), 22.5 (C-5), 18.4 (TIPS), 18.3 (TIPS), 18.2 (TIPS), 15.4 (C-8), 12.9 (TIPS), 12.1 (TIPS).

HR-MS (EI): calcd for $(C_{28}H_{58}O_4Si_2)^+$: 514.3874, found: 514.3848.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2891, 2866, 1739. 1463, 1435, 1384, 1365, 1257, 1194, 1166, 1127, 1100, 1068, 1013 cm^{-1}.



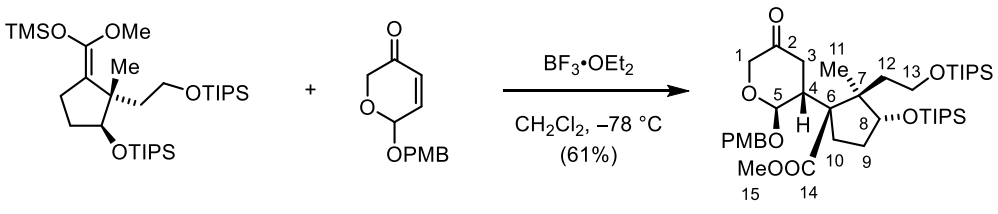
109 **97**

TMS ketene acetal 97. Diisopropylamine (0.499 mL, 3.53 mmol, 1.15 equiv) was dissolved in tetrahydrofuran (3 mL). The solution was cooled to −78 °C and *n*-butyllithium (2.31 M in hexane, 1.39 mL, 3.22 mmol, 1.05 equiv) was added dropwise. The solution was stirred for 10 min before it was allowed to warm to 0 °C. After 20 min, the solution was cooled to −78 °C and ester **109** (1.58 g, 3.07 mmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added over 5 min. Stirring was continued at −78 °C for 1 h. Freshly distilled chlorotrimethylsilane (0.412 mL, 3.22 mmol, 1.05 equiv) was added and after 1 h, the solution was allowed to warm to 25 °C. After 16 h, the solution was diluted with diethyl ether (15 mL) and the suspension was filtered through a short pad of celite covered with silica gel. The filter cake was rinsed with diethyl ether (70 mL) and the filtrate was concentrated to afford **97** (1.78 g, 99%) as a clear yellow oil. The crude product was used in the next step without further purification.

^{1}H NMR (800 MHz, C_6D_6) δ 4.23 (dd, *J* = 8.8, 5.5 Hz, 1H), 4.00 (td, *J* = 9.4, 6.5 Hz, 1H), 3.96 (td, *J* = 9.5, 6.1 Hz, 1H), 3.33 (s, 3H), 2.43 (ddd, *J* = 15.7, 8.2, 3.1 Hz, 1H), 2.28–2.10 (m, 2H), 2.06 (ddd, *J* = 15.5, 10.2, 7.7 Hz, 1H), 1.87–1.83 (m, 1H), 1.67 (ddt, *J* = 11.8, 10.1, 8.6 Hz, 1H), 1.35 (s, 3H), 1.20– 1.17 (m, 42H), 0.18 (s, 9H). **^{13}C NMR** (201 MHz, C_6D_6) δ 148.5, 104.7, 79.5, 61.7, 55.4, 46.2, 41.3, 32.2, 25.4, 21.6, 18.6, 18.5, 18.4, 13.1, 12.5, 0.2.

HR-MS (EI): calcd for $(C_{31}H_{66}O_4Si_3)^+$: 586.4269, found: 586.4266.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 2866, 2279, 1698, 1618, 1453, 1330, 1252, 1162, 1070 cm^{-1}.



97 **20** **96**

Mukaiyama−Michael adduct 96. Boron trifluoride diethyl ether complex (47 wt% in diethyl ether, 50.0 μL, 0.190 mmol, 1.05 equiv) was added dropwise to a solution of TMS ketene acetal **97** (145 mg, 0.254 mmol, 1.40 equiv) in a mixture of dichloromethane and diethyl ether (v/v = 9:1,

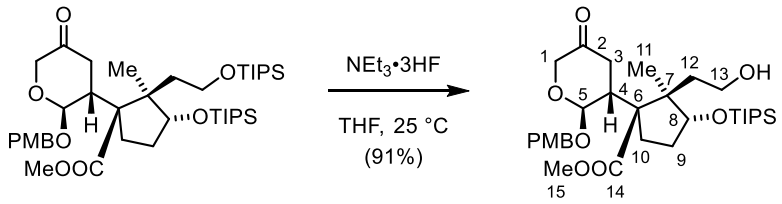
0.77 mL) at −78 °C. Enone **20** (42.5 mg, 0.181 mmol, 1 equiv) in a mixture of dichloromethane and diethyl ether (v/v = 9:1, 0.22 mL) was then added over two minutes. After 45 min, excess boron trifluoride diethyl ether complex was quenched by dropwise addition of saturated aqueous sodium bicarbonate solution (7 mL) at −78 °C. The mixture was allowed to warm to 25 °C and solid sodium bicarbonate was added until no further gas evolution was observed. The mixture was diluted with dichloromethane (3 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to yield a slightly yellow oil. The crude product was purified by flash column chromatography on silica gel (5% to 15% ethyl acetate in hexanes) to afford **96** (82.3 mg, 61%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.41 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H, PMB), 6.87 (d, *J* = 8.6 Hz, 2H, PMB), 5.64 (d, *J* = 3.9 Hz, 1H, H-5), 4.65 (d, *J* = 10.8 Hz, 1H, PMB), 4.44 (d, *J* = 10.9 Hz, 1H, PMB), 4.39 (dd, *J* = 8.2, 6.5 Hz, 1H, H-8), 4.10 (d, *J* = 17.9 Hz, 1H, H-1a), 3.87 (d, *J* = 17.9 Hz, 1H, H-1b), 3.85–3.75 (m, 2H, H-13), 3.81 (s, 3H, PMB), 3.68 (s, 3H, H-15), 2.56–2.34 (m, 3H, H-3, H-4), 2.22–2.13 (m, 1H, H-9a), 2.07 (ddd, *J* = 13.2, 10.2, 4.9 Hz, 1H, H-10a), 1.82 (ddd, *J* = 13.2, 10.3, 4.9 Hz, 1H, H-12a), 1.66–1.58 (m, 2H, H -10b, H-12b), 1.54–1.47 (m, 1H, H-9b), 1.10 (s, 3H, H-11), 1.06–1.02 (m, 42H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.9 (C-2), 175.5 (C-14), 159.4 (PMB), 129.9 (PMB), 129.7 (PMB), 113.9 (PMB), 99.0 (C-5), 79.5 (C-8), 69.7 (PMB), 65.6 (C-1), 60.9 (C-6), 60.3 (C-13), 55.4 (PMB), 51.7 (C-7), 51.4 (C-15), 45.3 (C-4), 41.7 (C-12), 38.5 (C-3), 31.4 (C-10), 31.0 (C-9), 18.4 (TIPS), 18.3 (TIPS), 18.2 (TIPS), 14.7 (C-11), 13.1 (TIPS), 12.2 (TIPS).

HR-MS (ESI): calcd for $(C_{41}H_{76}O_8Si_2)^+$ $(M+NH_4)^+$: 766.5104, found: 766.5129.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2892, 2866, 2362, 1726, 1614, 1587, 1516, 1464, 1388, 1358, 1303, 1250, 1205, 1180, 1096, 1069, 1035, 1013 cm^{-1}.



96 **110**

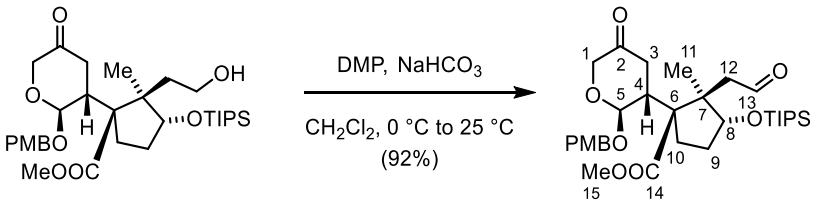
Alcohol 110. Triethylamine trihydrofluoride (1.50 mL, 9.20 mmol, 7.50 equiv) was added to a solution of Mukaiyama−Michael adduct **96** (919 mg, 1.23 mmol, 1 equiv) in tetrahydrofuran (6.1 mL) at 25 °C. After 18 h, saturated aqueous sodium bicarbonate (15 mL) was added dropwise. Solid sodium bicarbonate was then added until no further gas evolution was observed. The suspension was diluted with ethyl acetate (15 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a colorless oil and the crude was purified by flash column chromatography on silica gel (30% to 60% ethyl acetate in hexanes) to afford **110** (662 mg, 91%) as a colorless oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.35 (CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.21 (d, *J* = 8.6 Hz, 2H, PMB), 6.78 (d, *J* = 8.7 Hz, 2H, PMB), 5.87 (d, *J* = 4.4 Hz, 1H, H-5), 4.53 (d, *J* = 11.2 Hz, 1H, PMB), 4.48 (t, *J* = 8.2 Hz, 1H, H-8), 4.28 (d, *J* = 11.1 Hz, 1H, PMB), 4.11 (d, *J* = 17.7 Hz, 1H, H-1a), 3.86–3.77 (m, 1H, H-13a), 3.80 (d, *J* = 17.6 Hz, 1H, H-1b), 3.63 (ddd, *J* = 10.8, 7.9, 5.2 Hz, 1H, H-13b), 3.28 (s, 3H, PMB), 3.25 (s, 3H, H-15), 2.47 (dd, *J* = 14.2, 13.1 Hz, 1H, H-3a), 2.26 (dd, *J* = 14.2, 4.3 Hz, 1H, H-3b), 2.16 (dt, *J* = 13.1, 4.4 Hz, 1H, H-4), 2.07–1.98 (m, 1H, H-9a), 1.86–1.76 (m, 2H, H-10a, H-12a), 1.57 (dt, *J* = 13.6, 7.5 Hz, 1H, H-12b), 1.40–1.31 (m, 1H, H-9b), 1.12–0.99 (m, 25H, H-10b, H-11, TIPS), 0.47 (br s, 1H, OH). **^{13}C NMR** (101 MHz, C_6D_6) δ 210.0 (C-2), 175.1 (C-14), 160.0 (PMB), 130.5 (PMB), 129.7 (PMB), 114.2 (PMB), 98.1 (C-5), 80.8 (C-8), 69.0 (PMB), 65.5 (C-1), 60.6 (C-6), 59.4 (C-13), 54.8 (PMB), 51.5 (C-7), 51.1 (C-15), 46.1 (C-4), 41.4 (C-12), 38.6 (C-3), 31.9 (C-10), 30.5 (C-9), 18.4 (TIPS), 18.4 (TIPS), 13.8 (C-11), 13.4 (TIPS).

HR-MS (ESI): calcd for $(C_{24}H_{43}O_6Si)^-$ (M−OPMB)$^-$: 455.2623, found: 455.2834.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3444, 2946, 2867, 1724, 1614, 1587, 1516, 1464, 1390, 1359, 1303, 1250, 1205, 1176, 1100, 1067, 1034 cm^{-1}.



Aldehyde 111. Sodium bicarbonate (17.7 mg, 0.211 mmol, 5.00 equiv) was added to a solution of alcohol **110** (25.0 mg, 42.2 μmol, 1 equiv) in dichloromethane (0.5 mL). The suspension was cooled to 0 °C and Dess−Martin periodinane (26.8 mg, 63.3 μmol, 1.50 equiv) was added in one portion. The ice bath was removed and the mixture was stirred for 4.5 h at 25 °C. The suspension was then diluted with diethyl ether (10 mL) and was filtered through a short pad of celite. The filter cake was rinsed with diethyl ether (50 mL) and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **111** (22.9 mg, 92%) as a colorless solid. Recrystallization of the product from diethyl ether gave crystals suitable for single crystal X-ray diffraction analysis.

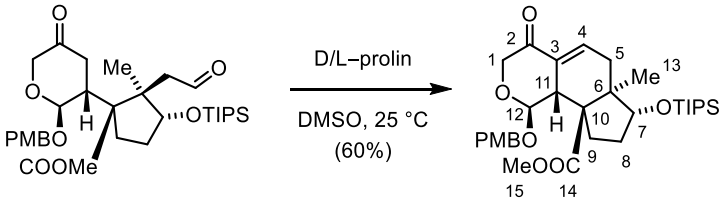
TLC (20% ethyl acetate in hexanes): R_f = 0.26 (CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 9.84 (dd, *J* = 3.6, 2.4 Hz, 1H, H-13), 7.22 (d, *J* = 8.6 Hz, 2H, PMB), 6.78 (d, *J* = 8.6 Hz, 2H, PMB), 5.76 (d, *J* = 4.3 Hz, 1H, H-5), 4.49–4.43 (m, 2H, H-8, PMB), 4.30 (d, *J* = 11.2 Hz 1H, PMB), 4.08 (d, *J* = 17.7 Hz, 1H, H-1a), 3.76 (d, *J* = 17.7 Hz, 1H, H-1b), 3.30 (s, 3H, PMB), 3.21 (s, 3H, H-15), 2.31 (t, *J* = 13.7 Hz, 1H, H-3a), 2.19−2.14 (m, 3H, H-3b, H-12), 2.07 (dt, *J* = 13.3, 4.4 Hz, 1H, H-4), 1.98–1.90 (m, 1H, H-9a), 1.88–1.81 (m, 1H, H-10a), 1.34–1.24 (m, 1H, H-9b), 1.22 (s, 3H, H-11) 1.08–0.97 (m, 22H, H-10b, TIPS). **^{13}C NMR** (101 MHz, C_6D_6) δ 209.6 (C-2), 200.2 (C-13), 174.6 (C-14), 160.2 (PMB), 131.0 (PMB), 129.2 (PMB), 114.3 (PMB), 97.2 (C-5), 79.1 (C-8), 68.8 (PMB), 65.4 (C-1), 59.5 (C-6), 54.8 (PMB), 51.8 (C-12), 51.6 (C-7), 51.3 (C-15), 46.3 (C-4), 38.3 (C-3), 31.7 (C-10), 29.4 (C-9), 18.4 (TIPS), 18.3 (TIPS), 14.8 (C-11), 13.1 (TIPS).

HR-MS (ESI): calcd for $(C_{32}H_{54}NO_8Si)^+$ $(M+NH_4)^+$: 608.3613, found: 608.3635.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2865, 1727, 1709, 1613, 1584, 1515, 1460, 1410, 1385, 1331, 1307, 1254, 1242, 1226, 1206, 1178, 1129, 1098, 1067, 1010 cm^{-1}.

Melting Point: 107−108 °C.



111 **112**

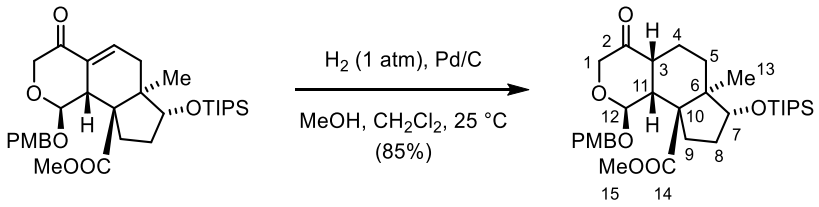
Enone 112. A 1:1 mixture of D-proline (108 mg, 0.941 mmol, 0.800 equiv) and L-proline (108 mg, 0.941 mmol, 0.800 equiv) was added to a solution of aldehyde **111** (492 mg, 1.18 mmol, 1 equiv) in degassed dimethyl sulfoxide (23.6 mL). After 24 h, before water (10 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The colorless crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **112** (405 mg, 60%) as a colorless liquid. Recrystallization of the product from diethyl ether gave crystals suitable for single crystal X-ray diffraction analysis.

TLC (20% ethyl acetate in hexanes): R_f = 0.29 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.22 (d, *J* = 8.6 Hz, 2H, PMB), 6.93 (dt, *J* = 6.3, 2.2 Hz, 1H, H-4), 6.79 (d, *J* = 8.6 Hz, 2H, PMB), 5.29 (d, *J* = 7.2 Hz, 1H, H-12), 4.67 (d, *J* = 11.3 Hz, 1H, PMB), 4.57 (dd, *J* = 8.9, 6.7 Hz, 1H, H-7), 4.37 (d, *J* = 11.3 Hz, 1H, PMB), 4.27 (d, *J* = 15.8 Hz, 1H, H-1a), 3.92 (d, *J* = 15.8 Hz, 1H, H-1b), 3.37–3.33 (m, 1H, H-11), 3.28 (s, 3H, PMB), 3.10 (s, 3H, H-15), 2.43–2.38 (m, 1H, H-5a), 2.36–2.29 (m, 1H, H-8a), 2.15–2.08 (m, 2H, H-5b, H-9a), 1.77 (ddd, *J* = 13.4, 11.9, 6.4 Hz, 1H, H-9b), 1.65–1.56 (m, 1H, H-8b), 1.11–1.01 (m, 21H, TIPS), 0.99 (s, 3H, H-13). **^{13}C NMR** (101 MHz, C_6D_6) δ 197.2 (C-2), 176.1 (C-14), 160.0 (PMB), 136.0 (C-4), 134.3 (C-3), 130.2 (PMB), 130.0 (PMB), 114.1 (PMB), 97.6 (C-12), 77.5 (C-7), 69.3 (PMB), 66.3 (C-1), 55.3 (C-10), 54.8 (PMB), 51.7 (C-15), 47.3 (C-6), 45.0 (C-11), 35.2 (C-5), 32.4 (C-8), 27.3 (C-9), 18.4 (TIPS), 18.3 (TIPS), 16.7 (C-13), 12.7 (TIPS).

HR-MS (ESI): calcd for $(C_{32}H_{52}NO_7Si)^+$ $(M+NH_4)^+$: 590.3508, found: 590.3512.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 2866, 2356, 1727, 1613, 1514, 1463, 1367, 1249, 1196, 1148, 1109, 1096, 1062, 1034 cm^{-1}.



112 **113**

Tricycle 113. Palladium on charcoal (10 wt%, 105 mg, 98.5 μmol, 0.15 equiv) was added to a solution of enone **112** (376 mg, 0.66 mmol, 1 equiv) in a mixture of methanol and dichloromethane (v/v = 10:1, 3.6 mL). The suspension was purged with hydrogen gas (1 atm) through a stainless steel needle for 1 min. Stirring of the suspension was then continued under a hydrogen atmosphere (1 atm) at 25 °C. After 3 h, hydrogen gas was released from the flask, the suspension was purged with argon and the mixture was filtered through a short pad of celite. The filter cake was rinsed with ethyl acetate (30 mL) and the filtrate was concentrated. The colorless crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **113** (319 mg, 85%) as a colorless solid.

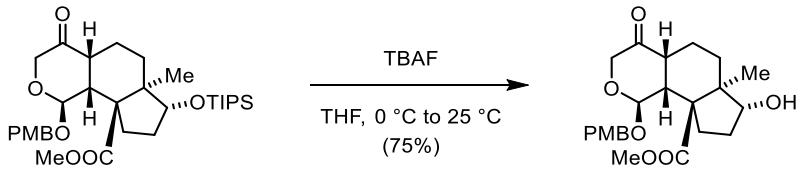
TLC (20% ethyl acetate in hexanes): R_f = 0.58 (CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.20 (d, *J* = 8.3 Hz, 2H, PMB), 6.77 (d, *J* = 8.3 Hz, 2H, PMB), 5.35 (d, *J* = 4.4 Hz, 1H, H−12), 4.89 (dd, *J* = 9.0, 6.4 Hz, 1H, H-7), 4.52 (d, *J* = 11.7 Hz, 1H, PMB), 4.35 (d, *J* = 11.7 Hz, 1H, PMB), 4.16 (d, *J* = 17.6 Hz, 1H, H-1a), 3.90 (d, *J* = 17.6 Hz, 1H, H-1b), 3.27 (s, 3H, PMB), 3.06 (s, 3H, H-15), 3.02 (dd, *J* = 6.4, 4.5 Hz, 1H, H-11), 2.62–2.56 (m, 2H, H-3, H-5a), 2.04–1.89 (m, 4H, H-4a, H-5b, H-8a, H-9a), 1.80–1.73 (m, 1H, H-9b), 1.71–1.68 (m, 1H, H-4b), 1.54–1.47 (m, 1H, H-8b), 1.18 (s, 3H, H-13), 1.13–1.01 (m, 21H, TIPS). **^{13}C NMR** (151 MHz, C_6D_6) δ 210.7 (C-2), 176.0 (C-14), 160.1 (PMB), 130.2 (PMB), 129.9 (PMB), 114.2 (PMB), 96.10 (C-12), 76.4 (C-7), 69.0 (PMB), 65.1 (C-1), 56.8 (C-10), 54.8 (PMB), 51.7(C-15), 47.8 (C-6), 45.9 (C-3), 44.0 (C-11), 31.2 (C-8), 30.0 (C-4), 27.8 (C-5), 22.9 (C-9), 18.4 (TIPS), 18.3 (TIPS), 16.0 (C-13), 12.76 (TIPS).

HR-MS (ESI): calcd for $(C_{32}H_{54}NO_7Si)^+$ $(M+NH_4)^+$: 592.3664, found: 592.3665.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2866, 2280, 1728, 1613, 1586, 1558, 1514, 1463, 1367, 1330, 1301, 1249, 1196, 1173, 1148, 1110, 1096, 1063, 1034 cm^{-1}.

Melting point: 116−121 °C.



113 **95**

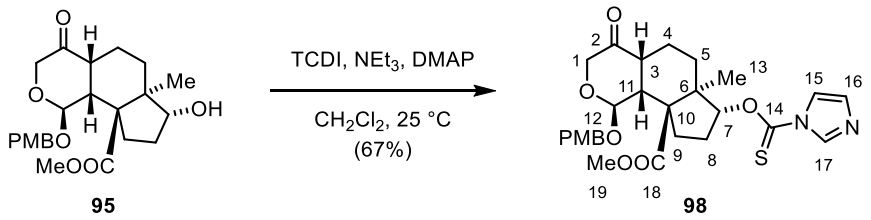
Alcohol 95. Tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 0.118 mL, 0.118 mmol, 1.02 equiv) was added to a solution of tricycle **113** (66.6 mg, 0.116 mmol, 1 equiv) in tetrahydrofuran (1 mL) at 0 °C. Upon completion of the addition, the solution was allowed to warm to 25 °C. After 6.5 h, saturated aqueous sodium bicarbonate solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford a colorless liquid. The crude product was purified by flash column chromatography on silica gel (30% to 50% ethyl acetate in hexanes) to afford **95** (36.4 mg, 75%) as a colorless liquid.

TLC (40% ethyl acetate in hexanes): R_f = 0.22 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.24 (d, *J* = 4.5 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.54 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.20 (d, *J* = 17.8 Hz, 1H), 4.00 (d, *J* = 17.8, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 2.75 (dd, *J* = 6.4, 4.4 Hz, 1H), 2.39–2.31 (m, 2H), 2.14–2.05 (m, 1H), 1.95–1.81 (m, 2H), 1.72–1.65 (m, 2H), 1.52–1.42 (m, 2H), 1.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.9, 175.9, 159.7, 130.2, 129.2, 114.0, 95.6, 75.9, 69.0, 65.0, 56.8, 55.5, 52.4, 46.6, 45.3, 43.2, 29.8, 29.0, 27.3, 22.6, 15.6.

HR-MS (ESI): calcd for $(C_{23}H_{34}NO_7)^+$ $(M+NH_4)^+$: 436.5245, found: 436.2337.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3434, 2951, 2838, 1725, 1612, 1586, 1514, 1461, 1368, 1302, 1247, 1196, 1176, 1147, 1128, 1109, 1089, 1032 cm^{-1}.



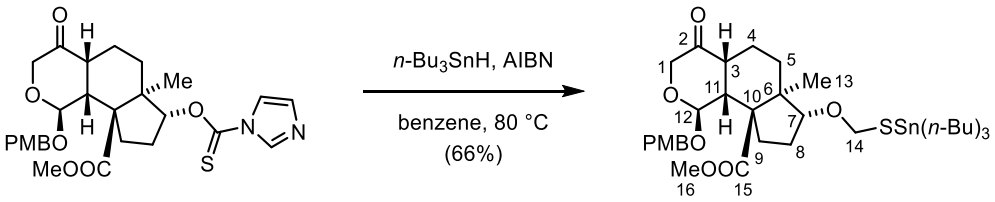
Thiocarbamate 98. 4-(Dimethylamino)pyridine (0.817 mg, 6.69 μmol, 0.200 equiv) and 1,1'-thiocarbonyldiimidazole (3.72 mg, 66.9 μmol, 2.00 equiv) were added to a solution of alcohol **95** (14.0 mg, 33.5 μmol, 1 equiv) in dichloromethane (1 mL). Triethylamine (5.11 μL, 36.8 μmol, 1.10 equiv) was then added and the reaction was stirred for 7 h at room temperature. The solution was then heated to 40 °C. After 17 h, the solvent was removed and the crude product was purified by flash column chromatography on silica gel (60% ethyl acetate in hexanes) to afford **98** (11.9 mg, 67%) as a yellow oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.22 (CAM).

^{1}H NMR (600 MHz, C_6D_6) δ 8.22 (s, 1H, H-17), 7.38 (t, *J* = 1.5 Hz, 1H, im), 7.18 (d, *J* = 8.6 Hz, 2H, PMB), 6.96 (dd, *J* = 1.6, 0.8 Hz, 1H, im) 6.79 (d, *J* = 8.6 Hz, 2H, PMB), 6.28 (dd, *J* = 9.6, 5.7 Hz, 1H, H-7), 5.17 (d, *J* = 4.1 Hz, 1H, H-12), 4.49 (d, *J* = 11.9 Hz, 1H, PMB), 4.33 (d, *J* = 11.9 Hz, 1H, PMB), 4.13 (d, *J* = 17.7 Hz, 1H, H-1a), 3.89 (dd, *J* = 17.8, 0.7 Hz, 1H, H-1b), 3.27 (s, 3H, PMB), 3.08 (dd, *J* = 6.6, 4.1 Hz, 1H, H-11), 3.04 (s, 3H, H-19), 2.47−2.41 (m, 2H, H-3, H-5a) 2.27−2.20 (m, 1H, H-8a), 1.79− 1.71 (m, 2H, H-4a, H-9a), 1.62− 1.53 (m, 2H, H-4b, H-9b), 1.25−1.19 (m, 2H, H-5b, H-8b), 0.84 (s, 3H, H-13). **^{13}C NMR** (151 MHz, C_6D_6) δ 210.0 (C-2), 184.1 (C-14), 175.0 (C-18), 160.2 (PMB), 136.4 (C-17), 131.5 (im), 130.3 (PMB), 129.5 (PMB), 118.5 (im), 114.2 (PMB), 95.2 (C-12), 87.5 (C-7), 68.6 (PMB), 65.0 (C-1), 57.2 (C-10), 54.8 (PMB), 52.1 (C-18), 47.1 (C-6), 45.5 (C-3), 43.6 (C-11), 29.8 (C-5), 27.6 (C-9), 27.1 (C-8), 22.5 (C-4), 17.1 (C-13).

HR-MS (ESI): calcd for $(C_{27}H_{32}N_2O_7S)^+$: 528.1930, found: 528.1908.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3132, 2952, 1726, 1612, 1585, 1514, 1463, 1386, 1335, 1285, 1246, 1196, 1175, 1147, 1129, 1107, 1074, 1026 cm^{-1}.



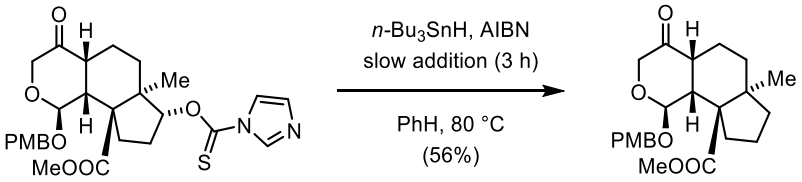
98 **114**

Tricycle 114. In a pressure flask, tributyltin hydride (31.7 μL, 118 μmol, 4.00 equiv) and azobis(isobutyronitrile) (1.00 mg, 5.88 μmol, 0.20 equiv) were added to a solution of thiocarbamate **98** (15.5 mg, 29.4 μmol, 1 equiv) in benzene (1.5 mL). The flask was sealed and the mixture was heated to 80 °C and after 30 min, the solution was cooled to 25 °C and was concentrated. The crude product was purified by flash column chromatography on previously deactivated silica gel (10% ethyl acetate in hexanes) to afford tricycle **114** (14.6 mg, 66%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.15 (UV, CAM).

^{1}H NMR (600 MHz, C_6D_6) δ 6.18 (d, ^2J = 8.5 Hz, 2H, PMB), 6.76 (d, ^2J = 8.5 Hz, 2H, PMB), 5.31 (d, $^3J_{12/11}$ = 4.4 Hz, 1H, H-12), 4.86 (d, $^2J_{14a/14b}$ = 2.1 Hz, 2H, H-14), 4.84−4.82 (m, 1H, H-7), 4.48 (d, ^2J = 11.6 Hz, 1H, PMB), 4.29 (d, ^2J = 11.7 Hz, 1H, PMB), 4.14 (d, ^2J = 17.6 Hz, 1H, H-1a), 3.89 (d, ^2J = 17.6 Hz, 1H, H-1b), 3.29 (s, 3H, PMB), 3.07 (s, 3H, H-16), 2.98 (dd, J = 6.5, 4.3 Hz, 1H, H-11), 2.74 (td, J = 13.1, 4.8 Hz, 1H, H-5a), 2.62 (dt, J = 13.6, 6.0 Hz, 1H, H-3), 2.12−2.05 (m, 1H, H-8a), 1.98−1.92 (m, 2H, H-4a, H-9a) 1.78−1.58 (m, 10H, H-4b, H-5b, H-9b, $SnBu_3$), 1.40−1.33 (m, 6H, $SnBu_3$), 1.22−1.17 (m, 9H, H-13, $SnBu_3$), 0.93 (app t, J = 7.3 Hz, 9H, $SnBu_3$). **^{13}C NMR** (151 MHz, C_6D_6) δ 210.6 (C-2), 175.6 (C-15), 160.0 (PMB), 130.3 (PMB), 129.8 (PMB) 114.1 (PMB), 95.9 (C-12), 81.9 (C-7), 69.7 (C-14), 68.9 (PMB), 65.1 (C-1), 57.1 (C-10), 54.8 (PMB), 51.8 (C-16), 46.8 (C-6), 45.7 (C-3), 43.8 (C-11), 30.5 (C-5), 29.1 ($SnBu_3$), 27.9 (C-8), 27.6 (C-9), 27.5 ($SnBu_3$), 22.7 (C-4), 16.7 (C-13), 13.9 ($SnBu_3$), 13.8 ($SnBu_3$).

HR-MS (ESI): not found.



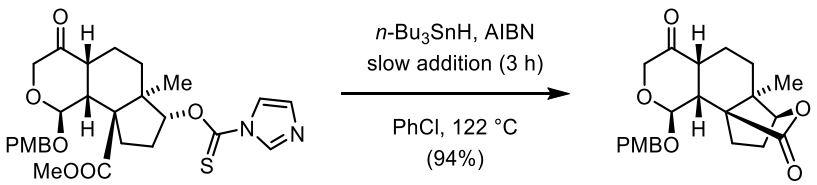
98 **115**

Tricycle 115. Thiocarbamate **98** (20.0 mg, 37.8 μmol, 1 equiv) was dissolved in degassed benzene (7.6 mL) and the solution was heated to 80 °C. A solution of tributyltin hydride (12.6 μL, 45.4 μmol, 1.20 equiv) and azobis(isobutyronitrile) (1.2 mg, 7.6 μmol, 0.2 equiv) in degassed benzene (1.9 mL) was added via syringe pump over 3 h. Upon completion of the addition, the solution was cooled to 25 °C and was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **115** (8.5 mg, 56%) as a colorless oil.

^{1}H NMR (600 MHz, C_6D_6) δ 7.20–7.16 (m, 2H), 6.81–6.74 (m, 2H), 5.19 (d, *J* = 4.4 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.15 (d, *J* = 17.6 Hz, 1H), 3.89 (dd, *J* = 17.6, 0.8 Hz, 1H), 3.28 (s, 3H), 3.11–3.06 (m, 4H), 2.68–2.58 (m, 2H), 2.28–2.18 (m, 1H), 2.02–1.96 (m, 1H), 1.91 (qd, *J* = 13.4, 4.9 Hz, 1H), 1.71–1.63 (m, 1H), 1.62–1.50 (m, 3H), 1.38–1.27 (m, 1H), 1.20–1.12 (m, 1H), 0.90 (s, 3H). **^{13}C NMR** (150 MHz, C_6D_6) δ 210.8, 175.6, 160.0, 130.2, 129.8, 114.1, 95.9, 68.8, 65.1, 57.6, 54.8, 51.5, 45.9, 44.0, 43.3, 36.3, 31.4, 29.2, 24.3, 23.1, 19.6.

HR-MS (ESI): calcd for $(C_{23}H_{34}O_6N)^+$ $(M+NH_4)^+$: 420.2386, found: 420.2391.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951, 1762, 1513, 1460, 1247, 1113, 1028 cm^{-1}.



98 **94**

Tetracycle 94. Thiocarbamate **98** (8.00 mg, 15.1 μmol, 1 equiv) was dissolved in chlorobenzene (3 mL) and the flask was evacuated and back-filled with argon three times. The solution was then placed in a pre-heated oil bath at 122 °C. A solution of tributyltin hydride (4.90 μL, 18.2 μmol, 1.2 equiv) and azobis(isobutyronitrile) (0.5 mg, 3.0 μmol, 0.2 equiv) in chlorobenzene (0.8 mL) was added via syringe pump over 3 h. Upon completion of the addition, the solution was cooled to

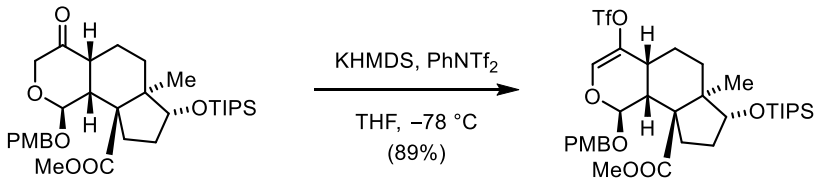
25 °C and was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **94** (5.5 mg, 94%) as a colorless oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.35 (weak by UV, CAM).

^{1}H NMR (600 MHz, C_6D_6) δ 7.17–7.11 (m, 2H), 6.82–6.75 (m, 2H), 4.79 (d, *J* = 6.3 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 11.7 Hz, 1H), 3.99 (d, *J* = 16.7 Hz, 1H), 3.73 (d, *J* = 16.7 Hz, 1H), 3.48 (s, 1H), 3.30 (d, *J* = 0.9 Hz, 3H), 2.90 (t, *J* = 5.9 Hz, 1H), 2.74 (dt, *J* = 13.0, 5.2 Hz, 1H), 1.54–1.40 (m, 2H), 1.38–1.26 (m, 3H), 1.24–1.09 (m, 2H), 0.90 (dt, *J* = 13.6, 3.3 Hz, 1H), 0.30 (s, 3H). **^{13}C NMR** (151 MHz, C_6D_6) δ 209.1, 177.8, 160.1, 130.3, 129.6, 114.1, 95.0, 83.0, 68.7, 65.4, 54.9, 53.5, 48.6, 45.2, 37.8, 28.4, 27.4, 23.2, 22.6, 15.2.

HR-MS (ESI): calcd for $(C_{22}H_{30}O_6N)^+$ $(M+NH_4)^+$: 404.2073, found: 404.2072.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950, 1772, 1729, 1613, 1514, 1458, 1330, 1248, 1030 cm^{-1}.



113 **117**

Triflate 117. To a solution of tricycle **113** (126 mg, 0.220 mmol, 1 equiv) in tetrahydrofuran (0.9 mL) was added a solution of potassium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.44 mL, 0.44 mmol, 2.0 equiv) dropwise at –78 °C. After 15 min, solid *N*-phenylbis(trifluoromethanesulfonimide) (141 mg, 0.400 mmol, 1.80 equiv) was added. After 30 min, saturated aqueous ammonium chloride solution (10 mL) and diethyl ether (10 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes) to afford **117** as a colorless oil (139 mg, 89%).

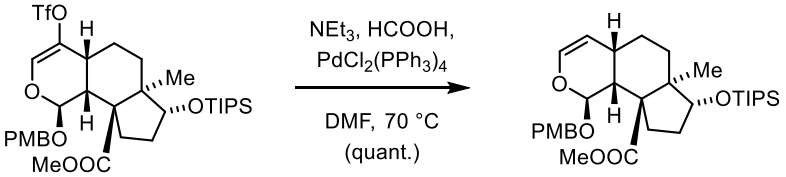
TLC (10% ethyl acetate in hexanes): R_f = 0.57 (CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 5.15 (d, *J* = 9.0 Hz, 1H), 4.94 (dd, *J* = 8.5, 6.6 Hz, 1H), 4.77 (d, *J* = 10.9 Hz, 1H), 4.29 (d, *J* = 10.9 Hz,

1H), 3.25 (s, 3H), 3.14 (s, 3H), 3.07 (dd, *J* = 9.0, 5.2 Hz, 1H), 2.84−2.75 (m, 1H), 2.62−2.50 (m, 2H), 2.05−2.85 (m, 3H), 1.55−1.43 (m, 3H), 1.15−1.05 (m, 21H), 0.98 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 175.9, 160.3, 138.1, 137.1, 130.4, 128.8, 120.8 (q, *J* = 320.4 Hz), 114.3, 100.4, 76.4, 71.2, 59.2, 54.8, 51.8, 47.6, 43.5, 36.6, 31.1, 29.3, 29.1, 25.0, 18.4, 18.4, 16.2, 12.8. **^{19}F NMR** (377 MHz, C_6D_6) δ −74.2.

HR-MS (EI): calcd for $(C_{33}H_{53}F_3NO_9SSi)^+$ $(M+NH_4)^+$: 724.3157, found: 724.3181.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2867, 1729, 1684, 1614, 1587, 1516, 1464, 1420, 1401, 1364, 1330, 1303, 1248, 1212, 1142, 1098, 1060, 1038 cm^{-1}.



117 **118**

Enol ether 118. To a solution of triflate **117** (48.4 mg, 68.5 µmol, 1 equiv) in dimethylformamide (0.7 mL) was added triethylamine (71 µL, 0.50 mmol, 7.5 equiv) and bis(triphenylphosphine)palladium(II) chloride (4.8 mg, 6.9 µmol, 0.10 equiv) and the solution was cooled to 0 °C. Formic acid (12.9 µL, 0.340 mmol, 5.00 equiv) was added and upon completion of the addition, the solution was allowed to warm to 25 °C. The solution then was heated to 70 °C. After 2 h, heating was ceased and the solution was cooled to 25 °C. Water (10 mL) and ethyl acetate (10 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **118** (38.2 mg, quant.) as a colorless oil.

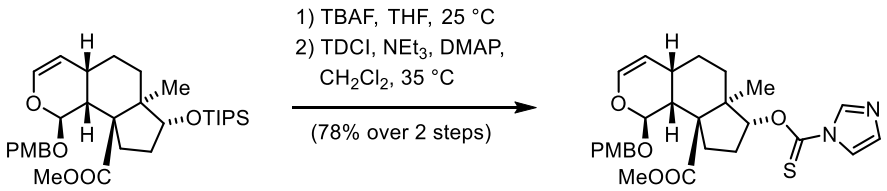
TLC (5% ethyl acetate in hexanes): R_f = 0.31 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.30 (dd, *J* = 5.9, 1.4 Hz, 1H), 5.36 (d, *J* = 9.0 Hz, 1H), 5.01 (dd, *J* = 9.0, 6.3 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 4.64 (dd, *J* = 5.9, 5.0 Hz, 1H), 4.45 (d, *J* = 10.9 Hz, 1H), 3.26 (s, 3H), 3.14 (s, 3H), 3.06 (dd, *J* = 9.0, 5.4 Hz, 1H), 2.98 (ddd, *J* = 13.5, 11.8, 7.7 Hz, 1H), 2.78 (td, *J* = 12.9, 4.8 Hz, 1H), 2.15–2.04 (m, 2H),

1.96 (dtd, *J* = 13.5, 9.1, 7.6 Hz, 1H), 1.68–1.49 (m, 4H), 1.20–1.12 (m, 24H). **^{13}C NMR** (101 MHz, C_6D_6) δ 176.8, 160.0, 140.8, 130.4, 129.8, 114.2, 107.2, 100.0, 76.7, 70.6, 59.7, 54.8, 51.5, 47.8, 44.7, 33.7, 31.4, 30.1, 29.7, 28.6, 18.5, 18.4, 16.6, 12.8.

HR-MS (ESI): calcd for $(C_{32}H_{50}O_6NSi)^+$ $(M+NH_4)^+$: 576.3720, found: 576.3729.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 2866, 1726, 1515, 1463, 1250, 1148, 1123, 1061 cm^{-1}.



118 **119**

Thiocarbamate 119. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 32 μL, 32 μmol, 1.1 equiv) was added dropwise to a solution of enol ether **118** (16 mg, 29 μmol, 1 equiv) in tetrahydrofuran (0.4 mL) at 25 °C. After 8.5 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford the alcohol (10.1 mg, 88%) as a white foam.

To a solution of the obtained alcohol (10.1 mg, 25.1 μmol, 1 equiv) in dichloromethane (0.5 mL) were added triethylamine (5.9 μL, 43 μmol, 1.7 equiv), 4-dimethylaminopyridine (0.6 mg, 5 μmol, 0.2 equiv) and 1,1'-thiocarbonylimidazole (13.9 mg, 77.8 μmol, 3.10 equiv) and the bright yellow solution was heated to 35 °C. After 13 h, heating was ceased and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **119** (11.4 mg, 89%) as a white foam.

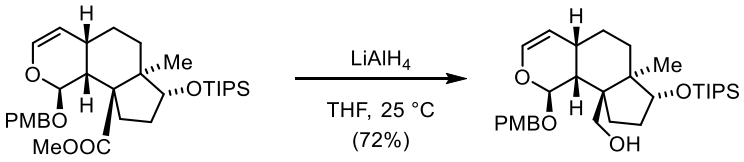
TLC (40% ethyl acetate in hexanes): R_f = 0.23 (UV, CAM).

^{1}H NMR (800 MHz, C_6D_6) δ 8.27 (s, 1H), 7.42 (s, 1H), 7.26–7.21 (m, 2H), 6.96 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.80–6.76 (m, 2H), 6.39 (dd, *J* = 9.6, 5.5 Hz, 1H), 6.28 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.22 (d, *J* = 9.0 Hz, 1H), 4.93 (d, *J* = 11.1 Hz, 1H), 4.59 (dd, *J* = 5.9, 4.9 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 3.27 (s, 3H), 3.10 (s, 3H), 3.07 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.78 (ddd, *J* = 13.8, 11.2, 9.0 Hz, 1H),

2.72–2.63 (m, 1H), 2.21 (dq, *J* = 14.8, 9.2 Hz, 1H), 1.97 (dddd, *J* = 13.2, 10.4, 4.5, 1.7 Hz, 2H), 1.47–1.43 (m, 1H), 1.34–1.24 (m, 3H), 0.82 (s, 3H). **^{13}C NMR** (200 MHz, C_6D_6) δ 184.2, 175.8, 160.2, 141.0, 136.4, 131.4, 130.3, 129.4, 118.5, 114.2, 107.0, 99.5, 88.4, 70.5, 59.9, 54.8, 51.9, 47.1, 44.4, 33.6, 30.0, 29.7, 28.0, 27.3, 18.2.

HR-MS (ESI): calcd for $(C_{27}H_{32}O_6N_2S)^-$ $(M–HCOO)^-$: 557.1958, found: 557.1960.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928, 1725, 1649, 1614, 1514, 1462, 1385, 1335, 1284, 1232, 1195, 1147 cm $^{-1}$.



118 **121**

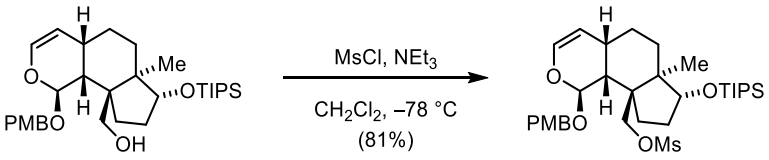
Alcohol 121. To a solution of ester **118** (35 mg, 63 μmol, 1 equiv) in tetrahydrofuran (0.6 mL) was added lithium aluminum hydride (4.8 mg, 13 μmol, 2.0 equiv). After 3 h, lithium aluminum hydride (2.4 mg, 6.5 μmol, 1 equiv) was added. After a total of 7.5 h, water (3 drops), followed by aqueous sodium hydroxide solution (10 wt%, 1 drop) and water (1 drop) were added. Solid sodium sulfate was added and after 10 min, the suspension was filtered through a short plug of celite. The filter cake was rinsed with diethyl ether (40 mL) and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **121** (24 mg, 72%) as a colorless oil.

TLC (25% ethyl acetate in hexanes): R_f = 0.35 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.40 (dd, *J* = 5.9, 1.4 Hz, 1H), 5.33 (d, *J* = 9.2 Hz, 1H), 4.97 (d, *J* = 10.9 Hz, 1H), 4.70 (t, *J* = 5.4 Hz, 1H), 4.47 (d, *J* = 10.9 Hz, 1H), 3.90 (dd, *J* = 8.8, 6.6 Hz, 1H), 3.47 (d, *J* = 10.8 Hz, 1H), 3.25 (s, 3H), 2.97 (d, *J* = 10.7 Hz, 1H), 2.86 (dd, *J* = 9.2, 5.9 Hz, 1H), 2.69–2.54 (m, 1H), 2.36–2.20 (m, 1H), 1.96–1.84 (m, 1H), 1.67–1.41 (m, 5H), 1.42–1.27 (m, 1H), 1.14–0.97 (m, 24H), 0.59 (s, 1H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.9, 140.7, 130.4, 130.1, 114.1, 107.4, 101.0, 78.8, 70.4, 63.8, 54.7, 50.7, 46.6, 41.0, 31.4, 30.6, 30.2, 28.2, 27.3, 18.4, 18.4, 16.2, 12.7.

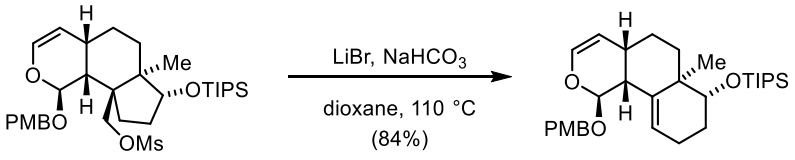
HR-MS (ESI): calcd for $(C_{31}H_{54}O_5NSi)^+$ $(M+NH_4)^+$: 548.3771, found: 548.3776.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3404, 2928, 2866, 1613, 1515, 1464, 1303, 1249, 1151, 1123, 1097 cm^{-1}.



121 **123**

Mesylate 123. Triethylamine (31 μL, 0.23 mmol, 5.0 equiv) was added to a solution of alcohol **121** (24 mg, 45 μmol, 1 equiv) in dichloromethane (0.4 mL) and the solution was cooled to –78 °C. Methane sulfonylchloride (11 μL, 14 μmol, 3.0 equiv) then was added dropwise. After 3 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and HPLC-grade dichloromethane (10 mL) and the suspension was allowed to warm to 25 °C. The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford **123** (22.4 mg, 81%) as a yellow solid, which was used without further purification for the next step.



123 **124**

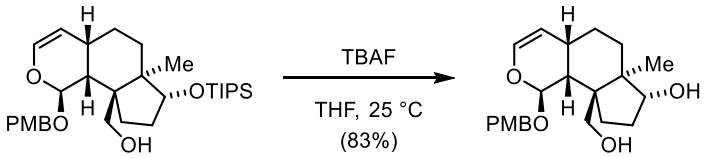
Alkene 124. To a solution of mesylate **123** (2.7 mg, 4.4 μmol, 1 equiv) in dioxane (0.4 mL) were added lithium bromide (3.9 mg, 44 μmol, 10 equiv) and sodium bicarbonate (3.7 mg, 44 μmol, 10 equiv) and the suspension was heated to 110 °C. After 18 h, lithium bromide (7.8 mg, 88 μmol, 20 equiv) and sodium bicarbonate (7.4 mg, 88 μmol, 20 equiv) were added and stirring at 110 °C was continued. After further 7 h, the solution was cooled to 25 °C and saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **124** (1.9 mg, 84%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.46 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.39 (d, *J* = 6.0 Hz, 1H), 5.53–5.46 (m, 1H), 5.09 (d, *J* = 9.0 Hz, 1H), 4.97 (d, *J* = 11.4 Hz, 1H), 4.68 (t, *J* = 5.5 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 3.69 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.26 (s, 3H), 2.79 (dd, *J* = 9.0, 5.9 Hz, 1H), 2.11 (dt, *J* = 13.1, 3.3 Hz, 1H), 2.00 (ddt, *J* = 13.3, 8.8, 5.4 Hz, 3H), 1.93–1.79 (m, 1H), 1.69–1.53 (m, 2H), 1.51–1.24 (m, 1H), 1.12 (m, 25H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.8, 141.1, 137.7, 130.5, 129.8, 126.4, 114.0, 106.5, 98.7, 79.7, 70.7, 54.7, 48.4, 40.2, 37.7, 36.0, 28.5, 28.2, 25.6, 18.6, 18.6, 18.4, 13.4.

HR-MS (ESI): calcd for $(C_{31}H_{52}O_5NSi)^+$ $(M+NH_4)^+$: 530.3660, found: 530.3667.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2866, 1647, 1514, 1463, 1355, 1248, 1160, 1104, 1062, 1039 cm^{-1}.



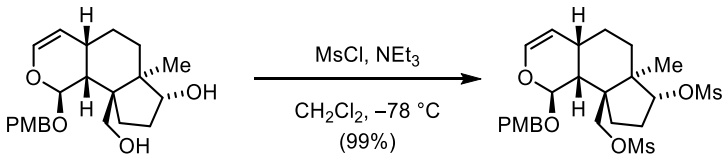
121 **125**

Diol 125. Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 33 µL, 33 µmol, 1.2 equiv) was added dropwise to a solution of TIPS ether **121** (14.5 mg, 27.3 µmol, 1 equiv) in tetrahydrofuran (0.6 mL) at 25 °C. After 14 h, tetrabutylammonium fluoride (1 M in tetrahydrofuran, 33 µL, 33 µmol, 1.2 equiv) was added. After additional 20 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) und ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (60% to 100% ethyl acetate in hexanes) to afford **125** (8.5 mg, 83%) as a white foam.

^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 6.38 (d, *J* = 5.8 Hz, 1H), 5.27 (d, *J* = 9.2 Hz, 1H), 4.94 (d, *J* = 11.0 Hz, 1H), 4.67 (t, *J* = 5.4 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 3.49 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.46–3.36 (m, 1H), 3.26 (s, 3H), 2.88 (d, *J* = 10.8 Hz, 1H), 2.83 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.58–2.43 (m, 1H), 2.27 (app dq, *J* = 11.7, 5.9 Hz, 1H), 1.87 (dtd, *J* = 13.8, 9.2, 6.8 Hz, 1H), 1.67–1.51 (m, 1H), 1.50–1.24 (m, 4H), 1.24–1.13 (m, 1H), 0.92 (s, 3H), 0.71 (br s, 2H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.9, 140.7, 130.4, 130.0, 114.1, 107.5, 100.9, 77.9, 70.3, 63.5, 54.7, 51.1, 45.6, 41.0, 30.5, 30.5, 29.4, 28.0, 27.1, 15.9.

HR-MS (ESI): calcd for $(C_{22}H_{34}O_5N)^+$ $(M+NH_4)^+$: 392.2437, found: 392.2434.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3385, 2929, 2868, 1656, 1612, 1514, 1464, 1303, 1248, 1235, 1150, 1039, 1012 cm^{-1}.



125 **126**

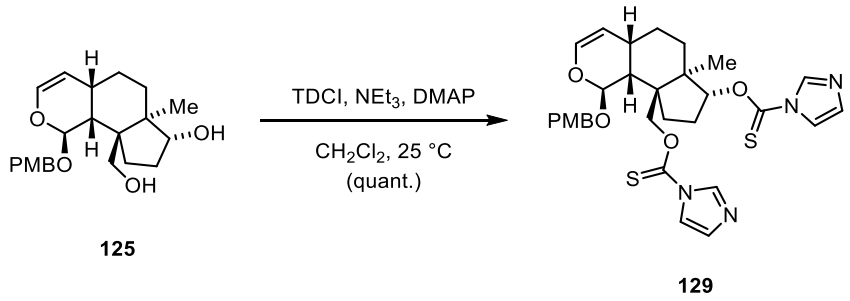
Dimesylate 126. Triethylamine (17 µL, 0.12 mmol, 8.0 equiv) was added to a solution of diol **125** (7.0 mg, 15 µmol, 1 equiv) in dichloromethane (0.4 mL) and the solution was cooled to –78 °C. Methanesulfonyl chloride (6.0 µL, 77 µmol, 5.0 equiv) was added dropwise. After 3 h, saturated aqueous sodium bicarbonate solution (10 mL) and HPLC-grade dichloromethane (10 mL) were added. The suspension was allowed to warm to 25 °C. The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **126** (8.1 mg, 99%) as a colorless oil.

TLC (50% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.20–7.17 (m, 2H), 6.78–6.70 (m, 2H), 6.28 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.08 (d, *J* = 9.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.63 (dd, *J* = 9.5, 6.4 Hz, 1H), 4.56 (t, *J* = 5.3 Hz, 1H), 4.36 (d, *J* = 11.1 Hz, 1H), 4.28–4.22 (m, 1H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.25 (s, 3H), 2.67–2.52 (m, 2H), 2.23 (dq, *J* = 11.9, 6.0 Hz, 1H), 2.12 (s, 3H), 2.10–2.04 (m, 1H), 2.02 (s, 3H), 1.79 (ddd, *J* = 13.7, 9.2, 2.3 Hz, 1H), 1.62–1.51 (m, 1H), 1.43 (dd, *J* = 12.7, 3.9 Hz, 1H), 1.34–1.27 (m, 1H), 1.25–1.09 (m, 2H), 0.91 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6) δ 160.1, 140.6, 130.6, 129.3, 114.2, 107.1, 99.7, 86.6, 70.4, 68.8, 54.8, 50.0, 46.1, 41.9, 37.6, 36.8, 30.3, 29.1, 27.3, 27.1, 27.1, 16.7.

HR-MS (ESI): calcd for $(C_{24}H_{38}O_9NS_2)^+$ $(M+NH_4)^+$: 548.1988, found: 548.1996.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 1515, 1352, 1250, 1174, 1041, 947 cm^{-1}.



125 **129**

Bisthiocarbamate 129. 1,1'-Thiocarbonyldiimidazole (17.3 mg, 87.6 µmol, 4.00 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 µmol, 0.2 equiv) were combined in a pressure tube and a solution of diol **125** (8.2 mg, 22 µmol, 1 equiv) in dichloromethane (0.5 mL), followed by triethylamine (6.7 µL, 48 µmol, 2.2 equiv) were added. The tube was sealed and the solution was heated to 40 °C. After 7 h, heating was ceased and the solution was cooled to 25 °C. The mixture was concentrated and the crude product was purified by flash column chromatography on silica gel (60% dichloromethane in ethyl acetate) to afford **129** (13.3 mg, quant.) as a slightly yellow oil.

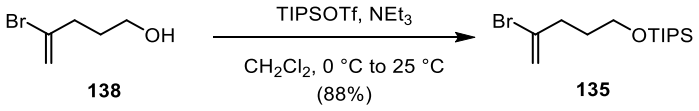
TLC (50% dichloromethane in ethyl acetate): R_f = 0.33 (UV, CAM).

^{1}H NMR (800 MHz, C_6D_6) δ 8.33 (s, 1H), 8.24 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 7.21–7.19 (m, 2H), 6.96 (app q, *J* = 0.9 Hz, 1H), 6.82 (app q, *J* = 0.8 Hz, 1H), 6.80–6.79 (m, 2H), 6.27 (dd, *J* = 6.0, 1.6 Hz, 1H), 5.42 (dd, *J* = 9.4, 6.2 Hz, 1H), 5.08 (d, *J* = 8.9 Hz, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.65 (dd, *J* = 11.1, 2.5 Hz, 1H), 4.56 (dd, *J* = 6.0, 4.9 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 10.9 Hz, 1H), 3.26 (s, 3H), 2.45–2.38 (m, 2H), 2.22–2.16 (m, 2H), 1.57–1.52 (m, 1H), 1.38–1.35 (m, 1H), 1.31–1.23 (m, 1H), 1.21–1.10 (m, 2H), 1.07–1.03 (m, 1H), 0.71 (s, 3H). **^{13}C NMR** (201 MHz, C_6D_6) δ 184.6, 184.2, 160.3, 140.8, 137.2, 136.4, 131.8, 131.7, 130.4, 129.3, 118.4, 117.7, 114.3, 106.7, 99.1, 89.0, 74.5, 70.3, 54.9, 50.2, 46.6, 43.1, 30.3, 30.2, 29.9, 27.7, 27.4, 26.6, 17.8.

HR-MS (ESI): calcd for $(C_{30}H_{35}O_5N_4S_2)^+$ $(M+H)^+$: 595.2094, found: 595.2058.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928, 1760, 1655, 1612, 1514, 1464, 1388, 1334, 1284, 1232, 1108, 1041, 988 cm^{-1}.

9.2.4 Experimental Procedures for Chapter 3.4



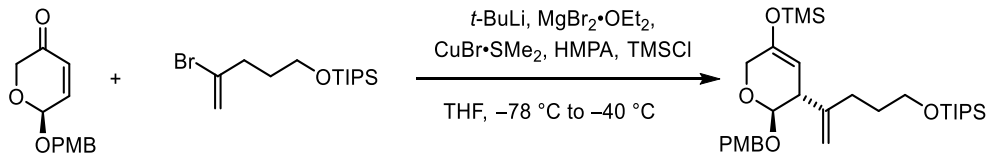
138 135

TIPS ether 135. Triethylamine (2.34 mL, 16.8 mmol, 2.10 equiv) was added to a solution of 4-bromo-4-penten-1-ol (**138**)[82] (1.32 g, 8.00 mmol, 1 equiv) in dichloromethane (40 mL) at 0 °C. Triisopropylsilyl trifluoromethanesulfonate (2.26 mL, 8.40 mmol, 1.05 equiv) was added dropwise. The solution was then allowed to warm to 25 °C. After 25 min, the solution was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3×100 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford **135** (2.26 g, 88%) as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.59 (q, *J* = 1.3 Hz, 1H), 5.40 (d, *J* = 1.6 Hz, 1H), 3.71 (t, *J* = 6.1 Hz, 2H), 2.54 (td, *J* = 7.3, 1.1 Hz, 2H), 1.79 (ddt, *J* = 8.4, 7.3, 6.2 Hz, 2H), 1.07–1.04 (m, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.6, 116.8, 61.9, 38.1, 31.4, 18.2, 12.1.

HR-MS (EI): calcd for $(C_{14}H_{30}{}^{79}BrO^{28}Si)^+$ $(M+H)^+$: 321.1244, found: 321.1289.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2866, 1630, 1463, 1383, 1105, 1059, 882 cm^{-1}.



20 135 139

TMS enol ether 139. To a solution of vinyl bromide **135** (1.67 g, 5.20 mmol, 1.30 equiv) in tetrahydrofuran (40 mL) was added a solution of *tert*-butyl lithium (1.70 M in pentanes, 5.65 mL, 9.60 mmol, 2.40 equiv) dropwise at –78 °C. After 45 min, solid magnesium bromide etherate (1.45 g, 5.60 mmol, 1.40 equiv) was added. After 45 min, copper(I) bromide dimethyl sulfide adduct (247 mg, 1.20 mmol, 0.300 equiv) was added. After 1 h, hexamethylphosphoramide (2.09 mL, 12.0 mmol, 3.00 equiv) was added. After 10 min, a solution of enone **20** (937 mg,

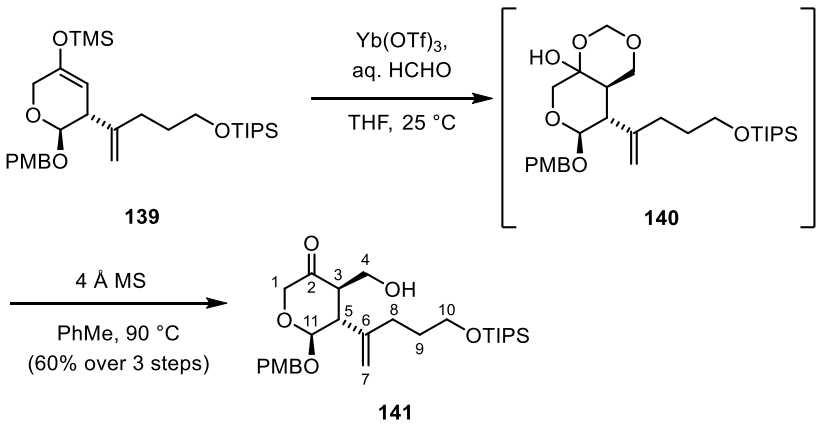
4.00 mmol, 1 equiv) and freshly distilled chlorotrimethylsilane (1.53 mL, 12.0 mmol, 3.00 equiv) in tetrahydrofuran (4 mL) was added dropwise. After 1 h, the solution was warmed to –40 °C and after 45 min, the solution was diluted with a mixture of saturated aqueous ammonium chloride solution and 25 wt% aqueous ammonia solution (v/v = 3:1, 60 mL) and diethyl ether (50 mL). The biphasic mixture was allowed to warm to 25 °C and after 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (3×150 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2×100 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford **139** as a slightly yellow oil, which was used without further purification immediately for the next step.

^{1}H NMR (400 MHz, C_6D_6) δ 7.29–7.23 (m, 2H), 6.81–6.75 (m, 2H), 5.19–5.15 (m, 1H), 5.05–5.01 (m, 1H), 4.93 (d, *J* = 4.6 Hz, 1H), 4.89 (d, *J* = 2.1 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.23 (d, *J* = 15.1 Hz, 1H), 4.05 (d, *J* = 14.8 Hz, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.29 (s, 3H), 3.24–3.20 (m, 1H), 2.38–2.23 (m, 2H), 1.75 (ddt, *J* = 16.4, 9.7, 6.6 Hz, 2H), 1.12 (d, *J* = 5.2 Hz, 21H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.8, 150.1, 148.5, 130.6, 129.7, 129.7, 114.1, 114.1, 112.1, 101.8, 99.2, 69.3, 63.4, 61.7, 54.7, 47.1, 31.8, 31.6, 18.4, 12.4, 0.2.

HR-MS (ESI): calcd for $(C_{30}H_{56}O_5NSi_2)^+$ $(M+NH_4)^+$: 566.3697, found: 566.3704.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2865, 1682, 1514, 1250, 1211, 1100, 1036 cm $^{-1}$.

$[\alpha]_{589}^{20}$ = +66.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



***β*-Hydroxy ketone 141.** To a solution of crude TMS enol ether **139** (assumed: 2.20 g, 4.00 mmol, 1 equiv) in tetrahydrofuran (31 mL) was added aqueous formaldehyde solution (37 wt% in water,

7.8 mL) and ytterbium triflate (192 mg, 0.40 mmol, 0.10 equiv) was added at 25 °C. After 14 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used without further purification for the next step.

The crude product was dissolved in toluene (20 mL) and the solution was added to Schlenk flask containing dry and activated 4 Å molecular sieves (2.46 g). The Schlenk flask was attached to a gas washing bottle containing water (15 mL) and the solution was heated to 90 °C under a constant stream of argon. After 5 h, heating was ceased and the solution was cooled to 25 °C. Saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL) were added and the biphasic mixture was filtered through a fritted glass funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×50 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on previously deactivated silica gel (7.5% triethylamine) (15% to 25% ethyl acetate in hexanes) to afford **141** (1.17 g, 58% over 3 steps) as a yellow oil.

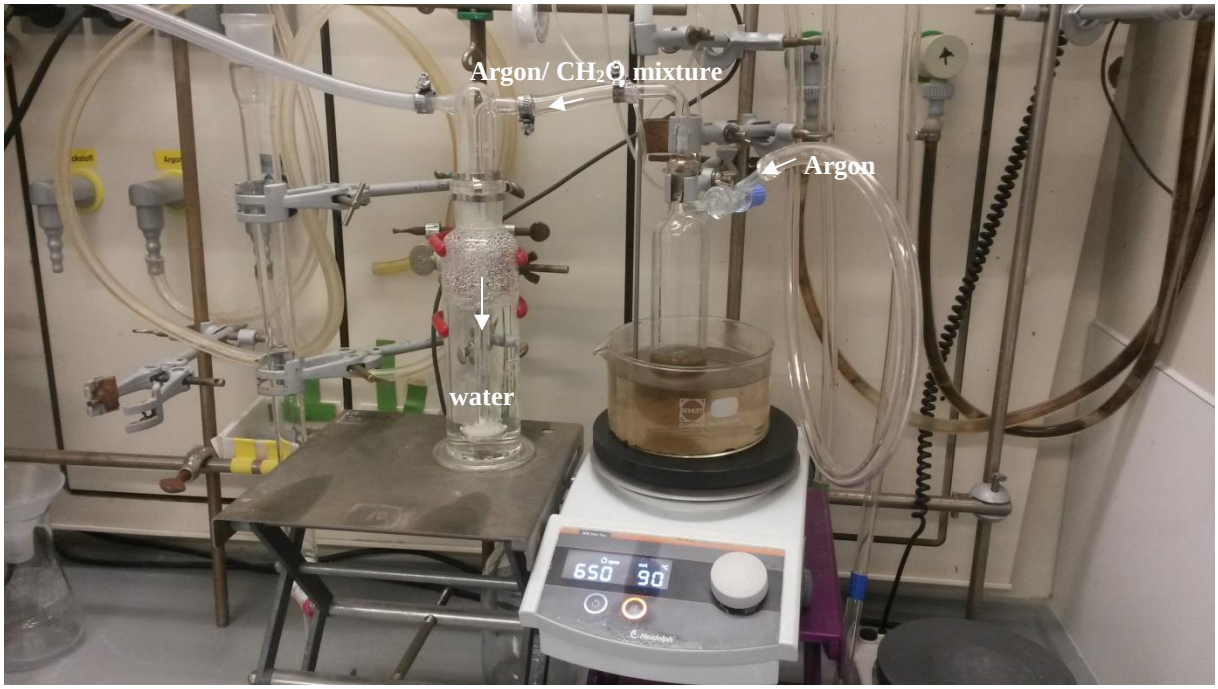


Figure 11. Setup for the formaldehyde gas outlet for the synthesis of *β*-hydroxy ketone **141**.

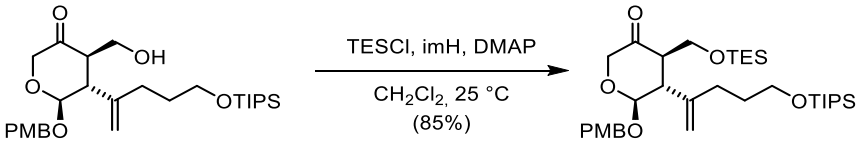
TLC (25% ethyl acetate in hexanes): R_f = 0.31 (UV, CAM).

^{1}H NMR (600 MHz, C_6D_6) δ 7.12–7.08 (m, 2H, PMB), 6.74 (d, ^3J = 8.6 Hz, 2H, PMB), 4.87–4.83 (m, 2H, H-11, H-7), 4.77–4.75 (m, 1H, H-7), 4.50 (d, ^2J = 11.7 Hz, 1H, PMB), 4.26 (d, ^2J = 11.7 Hz, 1H, PMB), 4.00 (d, $^2J_{1a/1b}$ = 17.5 Hz, 1H, H-1a), 3.83–3.75 (m, 1H, H-4a), 3.66 (d, $^2J_{1b/1a}$ = 17.5 Hz, 1H, H-1b), 3.52 (m, 3H, H-10, H-4b), 3.26 (s, 3H, PMB), 2.57 (dd, $^3J_{5/3}$ = 12.5 Hz, $^3J_{5/11}$ = 5.1 Hz, 1H, H-5), 2.47 (ddd, $^3J_{3/5}$ = 12.5 Hz, $^3J_{3/4}$ = 5.6, 2.8 Hz, 1H, H-3), 2.29 (t, $^3J_{OH/4}$ = 6.4 Hz, 1H, OH), 2.12–2.07 (m, 2H, H-8), 1.64–1.56 (m, 2H, H-9), 1.09–1.03 (m, 21H, TIPS). **^{13}C NMR** (150 MHz, C_6D_6) δ 212.7 (C-2), 159.9 (PMB), 147.6 (C-6), 129.9 (PMB), 129.7 (PMB), 114.1 (PMB), 112.5 (C-7), 102.0 (C-11), 69.5 (PMB), 66.5 (C-1), 63.0 (C-10), 59.1 (C-4), 54.8 (PMB), 49.7 (C-3), 48.2 (C-5), 31.5 (C-8), 31.2 (C-9), 18.3 (TIPS), 12.4 (TIPS).

HR-MS (ESI): calcd for $(C_{28}H_{50}O_6NSi)^+$ $(M+NH_4)^+$: 524.3407, found: 524.3407.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3494, 2941, 2865, 1725, 1613, 1514, 1463, 1248, 1105, 1033 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +71.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



141 **142**

TES ether 142. Imidazole (210 mg, 3.08 mmol, 2.60 equiv) was added to a solution of *β*-hydroxy ketone **141** (600 mg, 1.18 mmol, 1 equiv) in dimethylformamide (2.4 mL) at 25 °C. Chlorotriethylsilane (232 mg, 1.54 mmol, 1.30 equiv) was added. After 4 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **142** (624 mg, 85%) as a colorless oil.

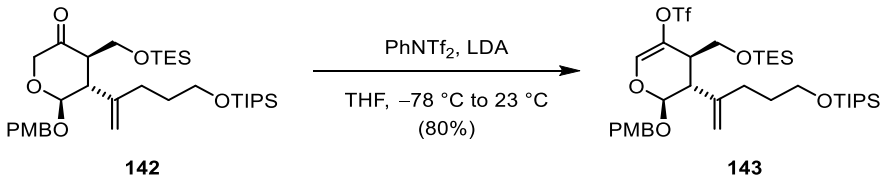
TLC (10% ethyl acetate in hexanes): R_f = 0.23 (UV, CAM).

^{1}H NMR (600 MHz, C_6D_6) δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.01 (s, 1H), 4.96 (d, *J* = 5.8 Hz, 1H), 4.89 (s, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.18–4.14 (m, 2H), 3.79 (d, *J* = 16.9 Hz, 1H), 3.68–3.64 (m, 3H), 3.31 (s, 3H), 3.04 (dd, *J* = 12.1, 5.8 Hz, 1H), 2.42 (ddd, *J* = 12.1, 3.8, 2.7 Hz, 1H), 2.29 (dq, *J* = 19.2, 8.2 Hz, 2H), 1.78 (tt, *J* = 7.7, 6.2 Hz, 2H), 1.15–1.10 (m, 21H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.70–0.61 (m, 6H). **^{13}C NMR** (150 MHz, C_6D_6) δ 208.0, 159.9, 148.4, 130.1, 129.8, 114.1, 112.0, 102.4, 69.4, 66.9, 63.3, 57.9, 54.8, 50.1, 47.1, 32.2, 31.4, 18.3, 12.4, 7.2, 4.8.

HR-MS (ESI): calcd for $(C_{34}H_{64}O_6NSi)^+$ $(M+NH_4)^+$: 638.4272, found: 638.4275.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2866, 1736, 1613, 1514, 1462, 1381, 1302, 1248, 1172, 1105, 1038 cm^{-1}.

$[\alpha]_{589}^{20}$ = +95.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



142 **143**

Vinyl triflate 143. A solution of *n*-butyl lithium (2.3 M in hexanes, 0.540 mL, 1.25 mmol, 1.25 equiv) was added dropwise to a solution of diisopropyl amine (0.18 mL, 1.3 mmol, 1.3 equiv) in tetrahydrofuran (1.7 mL) at –78 °C. After 10 min, the solution was allowed to warm to 0 °C. After 20 min at 0 °C, the solution was cooled to –78 °C and a solution of TES ether **142** (623 mg, 1.00 mmol, 1 equiv) was added dropwise. After 45 min, a solution of *N*-phenylbis(trifluoromethanesulfonimide) (502 mg, 1.40 mmol, 1.40 equiv) in tetrahydrofuran (1 mL) was added dropwise. The solution was slowly allowed to warm to 25 °C over 2 h. After 2 h at 25 °C, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% to 5% ethyl acetate in hexanes) to afford **143** (607 mg, 80%) as a colorless oil.

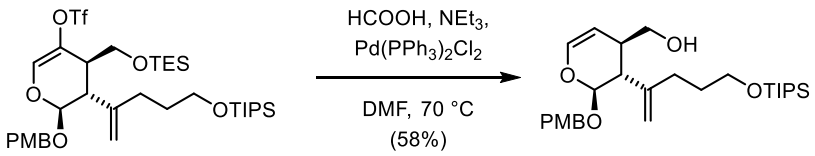
^{1}H NMR (800 MHz, C_6D_6) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 1.5 Hz, 1H), 5.01–4.96 (m, 2H), 4.87 (d, *J* = 5.6 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.29–4.25 (m, 1H),

3.96 (dd, *J* = 10.0, 5.8 Hz, 1H), 3.78 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.62 (t, *J* = 6.2 Hz, 2H), 3.30 (s, 3H), 3.09 (t, *J* = 6.0 Hz, 1H), 2.91–2.86 (m, 1H), 2.22 (dddd, *J* = 42.0, 15.5, 9.9, 5.6 Hz, 2H), 1.83–1.67 (m, 2H), 1.14–1.09 (m, 21H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.64–0.56 (m, 6H). **^{13}C NMR** (200 MHz, C_6D_6) δ 160.1, 147.2, 138.5, 135.4, 129.8, 128.4, 114.1, 112.1, 100.7, 70.9, 63.2, 60.0, 54.8, 44.1, 42.9, 32.8, 31.4, 18.3, 12.4, 7.0, 4.7.

HR-MS (ESI): calcd for $(C_{35}H_{63}O_8NF_3SSi_2)^+$ $(M+NH_4)^+$: 770.3765, found: 770.3779.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2867, 1514, 1421, 1398, 1247, 1208, 1141, 1099, 1067 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +39.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



143 **144**

Alkene 144. To a solution of triflate **143** (607 mg, 0.810 mmol, 1 equiv) in dimethylformamide (5.4 mL) was added bis(triphenylphosphine)palladium(II) chloride (57 mg, 0.081 mmol, 0.10 equiv), followed by triethylamine (0.500 mL, 3.63 mmol, 4.50 equiv). Formic acid (0.15 mL, 2.4 mmol, 3.0 equiv) was then added dropwise. The solution was heated to 70 °C. After 20 h, heating was ceased and water (20 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on previously deactivated silica gel (7.5% triethylamine) (30% ethyl acetate in hexanes) to afford **144** (230 mg, 58%) as a colorless oil.

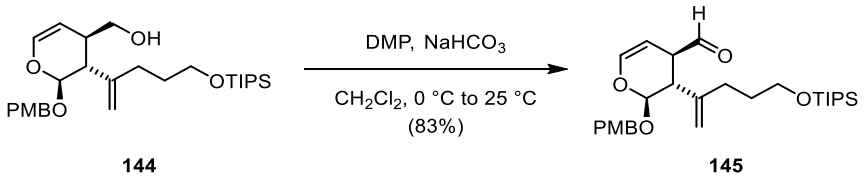
TLC (30% ethyl acetate in hexanes): R_f = 0.41 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.36 (dd, *J* = 6.2, 2.1 Hz, 1H), 4.96 (d, *J* = 1.4 Hz, 1H), 4.90–4.86 (m, 2H), 4.82 (d, *J* = 11.5 Hz, 1H), 4.73 (dd, *J* = 6.2, 2.8 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.61 (t, *J* = 6.2 Hz, 2H), 3.52 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.39–3.32 (m, 1H), 3.29 (s, 3H), 2.55 (dd, *J* = 7.7, 6.3 Hz, 1H), 2.33–2.26 (m, 1H), 2.27–2.18 (m, 2H), 1.82–1.64 (m, 2H), 1.13–1.07 (m, 21H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.9, 149.4, 141.8, 130.0, 129.8, 114.1, 110.6, 103.2, 100.4, 70.3, 65.1, 63.3, 54.8, 46.4, 39.8, 33.0, 31.5, 18.3, 12.4.

HR-MS (ESI): calcd for $(C_{28}H_{50}O_5NSi)^+$ $(M+NH_4)^+$: 508.3458, found: 508.3458.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3409, 2941, 2865, 1651, 1514, 1463, 1248, 1106, 1034 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +38.8 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



144 **145**

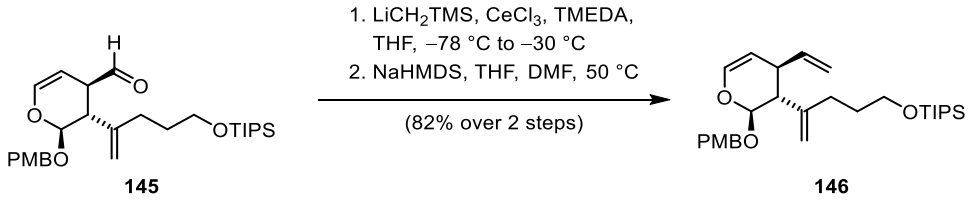
Aldehyde 145. Sodium bicarbonate (99.6 mg, 1.19 mmol, 5.00 equiv) was suspended in HPLC-grade dichloromethane (1.4 mL) and Dess–Martin periodinane (126 mg, 0.300 mmol, 1.50 equiv) was added. The solution was cooled to 0 °C and a solution of alcohol **144** (97 mg, 0.20 mmol, 1 equiv) in HPLC-grade dichloromethane (1 mL) was added. The suspension was then allowed to warm to 25 °C. After 3 h, diethyl ether (5 mL) was added and the suspension was filtered through a short plug of celite. The filter cake was rinsed with diethyl ether (15 mL). The filtrate was concentrated and the crude product was purified by quick flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **145** (80 mg, 83%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6) δ 9.46 (d, *J* = 1.1 Hz, 1H), 7.16–7.13 (m, 2H), 6.79–6.74 (m, 2H), 6.20 (dd, *J* = 6.2, 1.8 Hz, 1H), 5.01–4.90 (m, 3H), 4.75 (ddd, *J* = 6.3, 4.4, 0.8 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 3.56 (t, *J* = 6.2 Hz, 2H), 3.27 (s, 3H), 2.95 (app t, *J* = 4.0 Hz, 1H), 2.64–2.57 (m, 1H), 2.18–2.11 (m, 2H), 1.70–1.61 (m, 2H), 1.13–1.09 (m, 21H). **^{13}C NMR** (100 MHz, C_6D_6) δ 199.7, 159.8, 146.9, 141.9, 129.7, 129.6, 114.1, 111.6, 98.2, 97.6, 69.7, 63.0, 54.7, 47.1, 43.5, 32.5, 31.5, 18.3, 12.4.

HR-MS (ESI): calcd for $(C_{28}H_{48}O_5NSi)^+$ $(M+NH_4)^+$: 506.3302, found: 506.3299.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2865, 1727, 1654, 1613, 1514, 1463, 1248, 1104, 1036 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +26.8 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



Alkene 146. Anhydrous cerium(III) chloride (202 mg, 0.820 mmol, 5.00 equiv) was suspended in tetrahydrofuran (4.4 mL) and the suspension was stirred at 25 °C for 2 h. The suspension was sonicated for 5 min and was then cooled to –78 °C. A solution of (trimethylsilyl)methyllithium (1 M in pentanes, 0.66 mL, 0.66 mmol, 4.0 equiv) was slowly added dropwise. The yellow suspension was vigorously stirred for 30 min before a solution of aldehyde **145** (80 mg, 0.16 mmol, 1 equiv) in tetrahydrofuran (0.9 mL) was added dropwise. After 30 min, the solution was allowed to warm to –30 °C. After 2 h 30 min, tetramethylethylenediamine (0.25 mL, 1.64 mmol, 10.0 equiv) was added, followed by saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The biphasic mixture was allowed to warm to 25 °C. After 15 min, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (25 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford the alcohol (86 mg, 91%) as a 2:1 mixture of diastereomers.

The alcohol (86 mg, 0.15 mmol, 1 equiv) was dissolved in a mixture of tetrahydrofuran and dimethylformamide (v/v = 10:1, 12.4 mL) and a solution of sodium bis(trimethylsilyl)amide (1.0 M in toluene, 0.25 mL, 0.25 mmol, 1.7 equiv) was added dropwise. The solution was heated to 50 °C. After 1.5 h, heating was ceased and the solution was allowed to cool to 25 °C. Saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **146** (65.4 mg, 90%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.25 (UV, CAM).

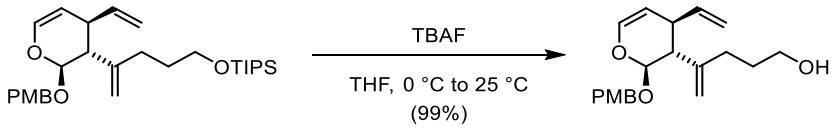
^{1}H NMR (400 MHz, C_6D_6) δ 7.26–7.20 (m, 2H), 6.81–6.74 (m, 2H), 6.35 (dd, *J* = 6.1, 2.2 Hz, 1H), 5.72 (ddd, *J* = 17.1, 10.1, 8.1 Hz, 1H), 5.05–4.98 (m, 2H), 4.94 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.84 (d, *J* = 7.7 Hz, 1H), 4.79 (s, 1H), 4.67 (dd, *J* = 6.1, 2.4 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.30 (s, 3H), 2.94–2.86 (m, 1H), 2.41 (dd, *J* = 9.5, 7.7 Hz, 1H), 2.31–2.13 (m, 2H), 1.83–1.63 (m, 2H), 1.15–1.06 (m, 21H). **^{13}C NMR** (100 MHz, C_6D_6) δ

159.8, 148.5, 141.3, 140.5, 130.1, 129.8, 114.9, 114.0, 110.7, 104.4, 101.4, 70.5, 63.3, 54.7, 50.3, 42.5, 33.5, 31.2, 18.3, 12.4.

HR-MS (ESI): calcd for $(C_{29}H_{50}O_4NSi)^+$ $(M+NH_4)^+$: 504.3509, found: 504.3509.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942, 2865, 1647, 1613, 1514, 1463, 1302, 1248, 1233, 1157, 1034 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20} = -2.4$ (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



146 **147**

Alcohol 147. Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 0.170 mL, 0.170 mmol, 1.05 equiv) was added dropwise to a solution of alkene **146** (80 mg, 0.16 mmol, 1 equiv) in tetrahydrofuran (1.4 mL) at 0 °C. Upon completion of the addition, the solution was allowed to warm to 25 °C. After 3 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **147** (53.6 mg, 99%) as a colorless oil.

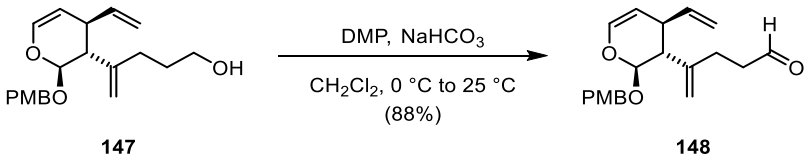
TLC (50% ethyl acetate in hexanes): R_f = 0.40 (UV, CAM).

^{1}H NMR (800 MHz, C_6D_6) δ 7.23–7.20 (m, 2H), 6.80–6.75 (m, 2H), 6.34 (dd, *J* = 6.1, 2.2 Hz, 1H), 5.66 (ddd, *J* = 17.1, 10.1, 8.1 Hz, 1H), 4.98 (ddd, *J* = 17.1, 1.8, 1.0 Hz, 1H), 4.92–4.89 (m, 2H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.79 (d, *J* = 7.9 Hz, 1H), 4.75 (s, 1H), 4.65 (dd, *J* = 6.1, 2.3 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 3.31 (t, *J* = 6.4 Hz, 2H), 3.28 (s, 3H), 2.86–2.81 (m, 1H), 2.35 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.10–1.97 (m, 2H), 1.57–1.47 (m, 2H), 0.56 (s, 1H). **^{13}C NMR** (200 MHz, C_6D_6) δ 159.9, 148.2, 141.3, 140.4, 130.0, 129.9, 115.0, 114.1, 110.9, 104.5, 101.2, 70.4, 62.3, 54.8, 50.4, 42.5, 33.2, 30.7.

HR-MS (ESI): calcd for $(C_{20}H_{30}O_4N)^+$ $(M+NH_4)^+$: 348.2175, found: 348.2167.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3364, 2937, 2874, 1648, 1613, 1514, 1248, 1233, 1108, 1031 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = −0.2 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



147 **148**

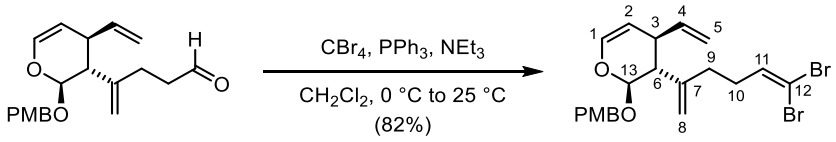
Aldehyde 148. Dess–Martin periodinane (96.3 mg, 0.230 mmol, 1.50 equiv) was added to a suspension of sodium bicarbonate (63.6 mg, 0.760 mmol, 5.00 equiv) in dichloromethane (1 mL) at 0 °C. A solution of alcohol **147** (50 mg, 0.15 mmol, 1 equiv) in dichloromethane (0.5 mL) was added dropwise and upon completion of the addition, the suspension was allowed to warm to 25 °C. After 3 h, diethyl ether (10 mL) was added and the suspension was filtered through a short plug of celite. The filter cake was rinsed with diethyl ether (50 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **148** (43.5 mg, 88%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6) δ 9.25 (t, *J* = 1.5 Hz, 1H), 7.18 (d, *J* = 9.1 Hz, 2H), 6.82–6.75 (m, 2H), 6.32 (dd, *J* = 6.1, 2.2 Hz, 1H), 5.56 (ddd, *J* = 17.1, 10.1, 8.0 Hz, 1H), 4.93 (ddd, *J* = 17.1, 1.8, 1.0 Hz, 1H), 4.88 (ddd, *J* = 10.1, 1.8, 0.6 Hz, 1H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.74 (s, 1H), 4.70 (d, *J* = 8.0 Hz, 1H), 4.64 (s, 1H), 4.61 (dd, *J* = 6.1, 2.2 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.28 (s, 3H), 2.79–2.70 (m, 1H), 2.25–2.09 (m, 3H), 2.05–1.95 (m, 2H). **^{13}C NMR** (100 MHz, C_6D_6) δ 200.4, 160.0, 147.0, 141.4, 140.0, 130.0, 129.8, 115.2, 114.1, 111.4, 104.3, 101.1, 70.5, 54.8, 50.2, 42.6, 41.3, 29.4.

HR-MS (ESI): calcd for $(C_{20}H_{28}O_4N)^+$ $(M+NH_4)^+$: 346.2018, found: 346.2011.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2909, 1723, 1648, 1612, 1514, 1248, 1233, 1109, 1031 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = -1.0 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



148 **132**

Dibromoalkene 132. A solution of triphenylphosphine (128 mg, 0.490 mmol, 4.00 equiv) in dichloromethane (0.4 mL) was added dropwise to a solution of carbon tetrabromide (80.8 mg, 0.240 mmol, 2.00 equiv) in dichloromethane (0.7 mL) at 0 °C. After 15 min, triethylamine (0.14 mL, 0.97 mmol, 8.0 equiv) was added and the solution turned pink. After 10 min, a solution of aldehyde **148** (40 mg, 0.12 mmol, 1 equiv) in dichloromethane (0.5 mL) was added dropwise. Upon completion of the addition, the brown solution was allowed to warm to 25 °C. After 3 h, saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **132** (48.5 mg, 82%) as a yellow oil.

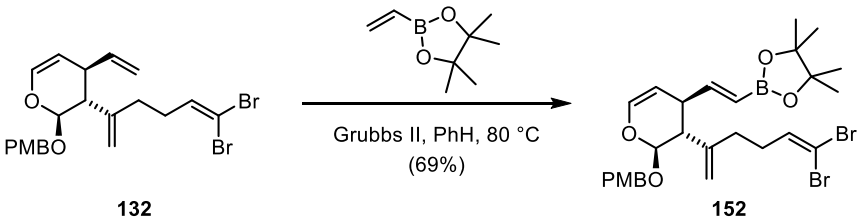
TLC (25% ethyl acetate in hexanes): R_f = 0.56 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.22–7.18 (m, 2H, PMB), 6.83–6.77 (m, 2H, PMB), 6.33 (dd, $^3J_{1/2}$ = 6.1 Hz, $^4J_{1/3}$ = 2.2 Hz, 1H, H-1), 6.07 (t, $^3J_{11/10}$ = 6.8 Hz, 1H, H-11), 5.58 (ddd, $^3J_{4/5}$ = 17.1 Hz, $^3J_{4/5}$ = 10.1, $^3J_{4/3}$ = 8.1 Hz, 1H, H-4), 4.99–4.88 (m, 2H, H-5), 4.83 (d, ^2J = 11.4 Hz, 1H, PMB), 4.76 (s, 1H, H-8a), 4.70 (d, $^3J_{13/6}$ = 8.0 Hz, 1H, H-13), 4.66 (s, 1H, H-8b), 4.62 (dd, $^3J_{2/1}$ = 6.1 Hz, $^3J_{2/3}$ = 2.2 Hz, 1H, H-2), 4.46 (d, ^2J = 11.5 Hz, 1H, PMB), 3.29 (s, 3H, PMB), 2.79–2.69 (m, 1H, H-3), 2.22 (dd, $^3J_{6/3}$ = 9.8 Hz, $^3J_{6/13}$ = 8.0 Hz, 1H, H-6), 2.03–1.94 (m, 2H, H-10), 1.90–1.80 (m, 2H, H-9). **^{13}C NMR** (100 MHz, C_6D_6) δ 160.0 (PMB), 147.0 (C-8), 141.4 (C-1), 140.1 (C-4), 138.8 (C-11), 130.0 (PMB), 129.8 (PMB), 115.3 (PMB), 114.1 (C-5), 111.4 (PMB), 104.3 (C-2), 101.1 (C-13), 89.1 (C-12), 70.5 (PMB), 54.8 (PMB), 50.1 (C-6), 42.6 (C-3), 34.7 (C-9), 30.9 (C-10).

HR-MS (EI): calcd for $(C_{21}H_{24}O_3{}^{79}Br_2)^+$: 482.0092, found: 482.0109.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2909, 1647, 1612, 1513, 1301, 1247, 1231, 1107, 1032 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = −4.6 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



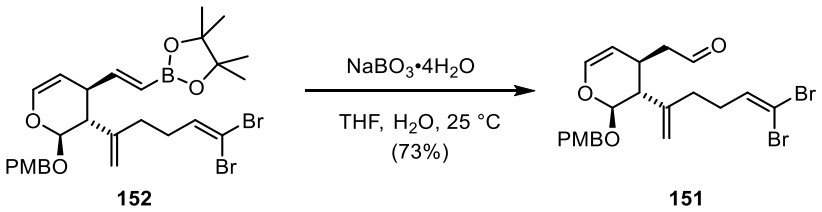
132 152

Boronic acid ester 152. To a solution of alkene **132** (8.00 mg, 16.5 µmol, 1 equiv) in benzene (0.4 mL) was added grubb's second generation catalyst (1.4 mg, 1.7 µmol, 0.10 equiv) at the solution was heated to 80 °C. After 2 h 15 min, the solution was cooled to 25 °C and was concentrated. The residue was purified by flash column chromatography on silica gel (5% to 30% ethyl acetate in hexanes) to afford **152** (7 mg, 69%) as slightly brown oil.

^{1}H NMR (400 MHz, C_6D_6) δ 7.22–7.17 (m , 2H), 6.83–6.73 (m, 3H), 6.28 (dd, *J* = 6.1, 2.2 Hz, 1H), 6.04 (t, *J* = 6.8 Hz, 1H), 5.76 (dd, *J* = 17.9, 1.1 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.72 (s, 1H), 4.68–4.60 (m, 3H), 4.43 (d, *J* = 11.6 Hz, 1H), 3.30 (s, 3H), 2.92–2.82 (m, 1H), 2.27 (dd, *J* = 9.8, 7.9 Hz, 1H), 1.99–1.89 (m, 2H), 1.89–1.75 (m, 2H), 1.07 (s, 12H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.9, 154.7, 146.8, 141.5, 138.9, 130.0, 129.9, 114.1, 111.6, 103.6, 101.0, 88.9, 83.1, 70.4, 54.8, 49.6, 44.0, 34.9, 30.9, 25.0, 25.0. (signal for C5 is missing, verified by HSQC).

HR-MS (EI): calcd for $(C_{27}H_{35}O_5{}^{11}B^{79}Br_2)^+$: 608.0939, found: 608.0971.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977, 2927, 1634, 1514, 1358, 1323, 1249, 1144 cm^{-1}.



152 151

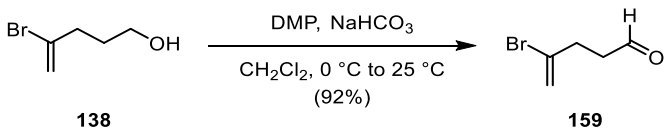
Aldehyde 151. Sodium perborate tetrahydrate (1.94 mg, 12.6 µmol, 1.10 equiv) was added to a solution of boronic acid ester **152** (7.00 mg, 11.5 µmol, 1 equiv) at 25 °C. After 4 h 45 min, water (10 mL) and diethyl ether (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **151** (4.2 mg, 73%) as a slightly yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.43 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 9.24 (t, *J* = 1.4 Hz, 1H), 6.82–6.77 (m, 2H), 6.23 (dd, *J* = 6.2, 2.1 Hz, 2H), 6.03 (t, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.71–4.66 (m, 3H), 4.57 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 3.30 (s, 3H), 2.56 (app tdd, *J* = 8.6, 5.0, 2.5 Hz, 1H), 2.16 (ddd, *J* = 17.4, 5.0, 1.2 Hz, 1H), 2.06 (dd, *J* = 8.8, 7.0 Hz, 1H), 1.96 (q, *J* = 7.6 Hz, 2H), 1.89–1.67 (m, 4H). **^{13}C NMR** (100 MHz, C_6D_6) δ 199.8, 160.0, 146.7, 140.9, 138.6, 130.1, 129.7, 114.2, 112.0, 104.5, 100.2, 89.4, 70.3, 54.8, 49.4, 48.1, 33.5, 31.0, 31.0.

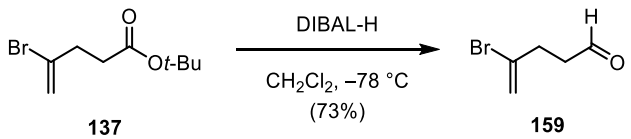
HR-MS (EI or ESI): not found.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928, 1722, 1649, 1613, 1514, 1248, 1112 cm^{-1}.



138 **159**

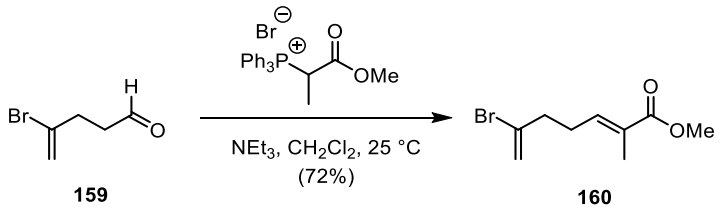
4-Bromopent-4-enal (159). To a solution of 4-bromo-4-penten-1-ol (**138**)[82] (385 mg, 2.33 mmol, 1 equiv) in HPLC-grade dichloromethane (12 mL) was added solid sodium bicarbonate (980 mg, 11.7 mmol, 5.00 equiv) and the suspension was cooled to 0 °C. Dess–Martin periodinane (1.39 g, 3.27 mmol, 1.40 equiv) was added in one portion. After 5 min, the suspension was allowed to warm to 25 °C. After 3 h, the solution was diluted with diethyl ether (20 mL), the suspension was filtered through a short plug of celite and the filter cake was rinsed with diethyl ether (20 mL). The filtrate was concentrated und the crude product was purified by flash column chromatography on silica gel (30% diethyl ether in pentanes) to afford **159** (349 mg, 92%) as a volatile brownish oil. The product was isolated as a 69 wt% solution in diethyl ether and was immediately used as received for the next step.



137 **159**

Alternative preparation of 4-bromopent-4-enal (159). Di-*iso*-butylaluminum hydride (1.0 M in dichloromethane, 24.0 mL, 24.0 mmol, 1 equiv) was added dropwise via syringe pump (addition rate: 50 mL/h) to a solution of ester **137** (5.65 g, 24.0 mmol, 1 equiv) in dichloromethane (121 mL) at –78 °C. After 50 min, saturated aqueous Rochelle salt solution (50 mL) was added dropwise and

the suspension was allowed to slowly warm to 0 °C. Ethyl acetate (200 mL) and water (50 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×250 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (150 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography (30% diethyl ether in pentanes) to afford **159** (2.84 g, 73%) as a slightly yellow oil.



159 160

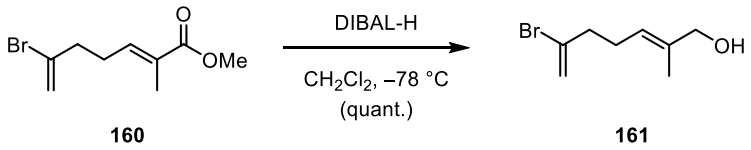
Methyl (*E*)-6-bromo-3-methylhepta-2,6-dienoate (160). To a solution of 1-methoxycarbonylethyltriphenylphosphonium bromide[162] (1.56 g, 3.64 mmol, 1.70 equiv) in dichloromethane (7.4 mL) was added triethylamine (0.89 mL, 6.4 mmol, 3.0 equiv) dropwise at 25 °C. After 20 min, a solution of 4-bromopent-4-enal (**159**) (349 mg, 2.14 mmol, 1 equiv) in dichloromethane (1.8 mL) was added dropwise. After 1 h, saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (25 mL), the washed solution was dried over sodium sulfate and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes) to afford **160** (358 mg, 72%) as a colorless oil.

TLC (3% ethyl acetate in hexanes): R_f = 0.17 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80–6.63 (m, 1H), 5.68–5.56 (m, 1H), 5.49–5.32 (m, 1H), 3.73 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 1.89–1.83 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 139.8, 133.2, 129.0, 117.6, 51.9, 40.3, 27.3, 12.7.

HR-MS (EI): calcd for $(C_9H_{13}O_2{}^{79}Br)^+$: 232.0093, found: 232.0095.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950, 1714, 1629, 1435, 1268, 1197, 1144, 1112 cm^{-1}.



160 161

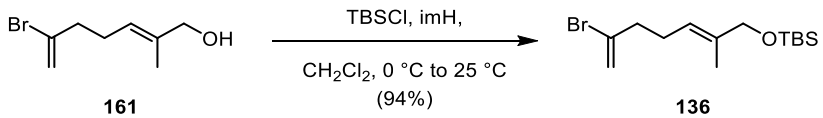
(*E*)-6-Bromo-3-methylhepta-2,6-dien-1-ol (161). To a solution of methyl (*E*)-6-bromo-3-methylhepta-2,6-dienoate (**160**) (345 mg, 1.48 mmol, 1 equiv) in dichloromethane (7.4 mL) was added dropwise a solution of di-*iso*-butylaluminum hydride (1.0 M in dichloromethane, 3.7 mL, 3.7 mmol, 2.5 equiv) at –78 °C. After 40 min, a solution of saturated aqueous ammonium chloride (6.5 mL) was added, followed by a mixture of ethyl acetate and hexanes (v/v = 1:1, 12 mL). The solution was allowed to slowly warm to 25 °C and saturated aqueous Rochelle salt solution (12 mL) was added. The solution was stirred at 25 °C for 20 min. The layers then were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **161** (305 mg, quant.) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.22 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (q, *J* = 1.3 Hz, 1H), 5.43–5.36 (m, 2H), 4.06–3.97 (m, 2H), 2.48 (ddd, *J* = 7.3, 6.5, 1.0 Hz, 2H), 2.36–2.27 (m, 2H), 1.69 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.4, 134.1, 123.7, 116.9, 68.8, 41.3, 26.3, 13.9.

HR-MS (EI): calcd for $(C_8H_{11}{}^{79}Br)^+$: 186.0039, found: 186.0047.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3312, 2914, 2860, 1629, 1430, 1180, 1118, 1064, 1005 cm^{-1}.



161 136

TBS ether 136. Imidazole (142 mg, 2.09 mmol, 1.40 equiv) was added to a solution of (*E*)-6-bromo-3-methylhepta-2,6-dien-1-ol (**161**) (305 mg, 1.49 mmol, 1 equiv) in dichloromethane (3 mL) and the solution was cooled to 0 °C. *Tert*-butyldimethylchlorosilane (292 mg, 1.94 mmol, 1.30 equiv) was added in one portion and the solution was allowed to warm to 25 °C. After 16 h, saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (15 mL) were added, the layers were separated and the aqueous layer was extracted with dichloromethane (3×15 mL).

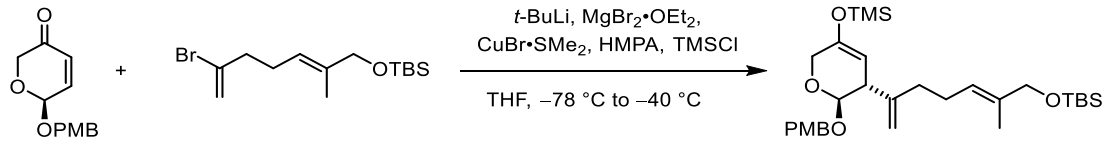
The combined organic layers were washed with brine (15 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes) to afford **136** (446 mg, 94%) as a colorless oil.

TLC (3% ethyl acetate in hexanes): R_f = 0.48 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, *J* = 1.4 Hz, 1H), 5.43–5.33 (m, 2H), 4.01 (s, 2H), 2.50–2.43 (m, 2H), 2.35–2.25 (m, 2H), 1.62 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.0, 134.4, 122.1, 116.8, 68.5, 41.5, 26.3, 26.1, 18.6, 13.7, −5.1.

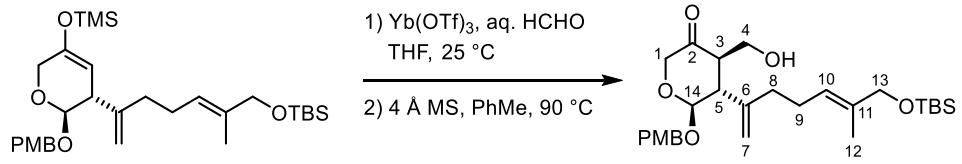
HR-MS (EI): calcd for $(C_{13}H_{24}O^{79}Br^{28}Si)^+$: 303.0774, found: 303.0768.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2856, 1629, 1462, 1471, 1251, 1110, 1066 cm^{-1}.



20 **136** **162**

TMS enol ether 162. To a solution of vinyl bromide **136** (415 mg, 1.30 mmol, 1.30 equiv) in tetrahydrofuran (10 mL) was added a solution of *tert*-butyl lithium (1.49 M in pentanes, 1.61 mL, 2.40 equiv) dropwise at –78 °C. After 45 min, solid magnesium bromide etherate (362 mg, 1.40 mmol, 1.40 equiv) was added. After 45 min, copper(I) bromide dimethyl sulfide adduct (62 mg, 0.30 mmol, 0.30 equiv) was added. After 1 h, hexamethylphosphoramide (538 mg, 3.00 mmol, 3.00 equiv) was added. After 10 min, a solution of enone **20** (234 mg, 1.00 mmol, 1 equiv) and freshly distilled chlorotrimethylsilane (0.38 mL, 3.0 mmol, 3.0 equiv) in tetrahydrofuran (6 mL) was added dropwise. After 1 h, the solution was warmed to –40 °C and after 45 min, the solution was diluted with a mixture of saturated aqueous ammonium chloride solution and 25 wt% aqueous ammonia solution (v/v = 3:1, 20 mL) and diethyl ether (10 mL). The biphasic mixture was allowed to warm to 25 °C and after 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford **162** as a slightly yellow oil, which was used without further purification immediately for the next step.



162 **163**

***β*-Hydroxy ketone 163.** To a solution of crude TMS enol ether **162** (assumed: 547 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (7.8 mL) was added aqueous formaldehyde solution (37 wt% in water, 1.95 mL) and ytterbium triflate (45 mg, 0.10 mmol, 0.10 equiv) was added at 25 °C. After 14 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2×100 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used without further purification for the next step.

The crude product was dissolved in toluene (5 mL) and the solution was added to Schlenk flask containing dry and activated 4 Å molecular sieves (617 mg). The Schlenk flask was attached to a gas washing bottle containing water (25 mL) and the solution was heated to 90 °C. After 5 h, heating was ceased and the solution was cooled to 25 °C. Saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL) were added and the biphasic mixture was filtered through a fritted glass funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×100 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on previously deactivated silica gel (7.5% triethylamine) (25% ethyl acetate in hexanes) to afford **163** (235 mg, 47% over 3 steps) as a yellow oil.

TLC (25% ethyl acetate in hexanes): R_f = 0.28 (UV, CAM).

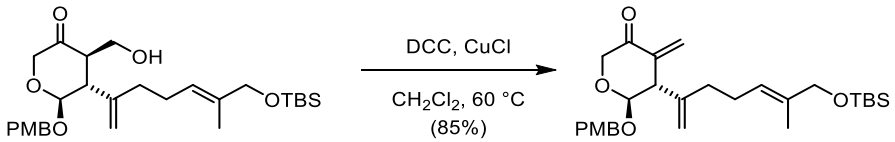
^{1}H NMR (599 MHz, $CDCl_3$) δ 7.14 (d, ^3J = 8.7 Hz, 2H, PMB), 6.78 (d, ^3J = 8.7 Hz, 2H, PMB), 5.44 (ddt, J = 7.0, 5.5, 1.4 Hz, 1H, H-10), 4.89–4.86 (m, 1H, H-7a), 4.85 (d, $^3J_{14/5}$ = 5.1 Hz, 1H, H-14), 4.82–4.79 (m, 1H, H-7b), 4.54 (d, ^2J = 11.7 Hz, 1H, PMB), 4.30 (d, ^2J = 11.7 Hz, 1H, PMB), 4.05 (d, $^2J_{1a/1b}$ = 17.5 Hz, 1H, H-1a), 4.00–3.98 (m, 2H, H-13), 3.82 (ddd, J = 14.6, 6.6, $^3J_{4a/3}$ = 2.9 Hz, 1H, H-4a), 3.70 (d, $^2J_{1b/1a}$ = 17.5 Hz, 1H, H-1b), 3.54 (dt, J = 11.7, 6.0 Hz, 1H, H-4b), 3.30 (s, 3H, PMB), 2.59 (dd, $^3J_{5/3}$ = 12.5 Hz, $^3J_{5/14}$ = 5.1 Hz, 1H, H-5), 2.45 (ddd, $^3J_{3/5}$ = 12.5 Hz, $^3J_{3/4b}$ = 5.8 Hz, $^3J_{3/4a}$ = 2.9 Hz, 1H, H-3), 2.29 (t, $^3J_{OH/4}$ = 6.9 Hz, 1H, OH), 2.16–2.10 (m, 2H, H-9), 2.02 (td, $^3J_{8/9}$ = 6.9 Hz, $^4J_{8/10}$ = 2.0 Hz, 2H, H-8), 1.58 (s, 3H, H-12), 1.00 (s, 9H, TBS), 0.09 (s, 6H, TBS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.6 (C-2), 159.9 (PMB), 147.3 (C-6), 135.4 (C-11), 129.9

(PMB), 129.7 (PMB), 124.1 (C-10), 114.2 (PMB), 112.7 (C-7), 101.8 (C-14), 69.4 (PMB), 68.8 (C-13), 66.5 (C-2), 59.1 (C-4), 54.8 (PMB), 49.5 (C-3), 48.1 (C-5), 35.0 (C-8), 26.2 (TBS), 25.8 (C-9), 18.6 (TBS), 13.6 (C-12), −5.1 (TBS).

HR-MS (ESI): calcd for $(C_{28}H_{48}O_6NSi)^+$ $(M+NH_4)^+$: 522.3251, found: 522.3257.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3496, 2954, 2929, 2856, 2280, 1724, 1613, 1514, 1462, 1302, 1248, 1173, 1067, 1032 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +80.0 (c = 1.0 · 10 g · mL-1, CH_2Cl_2).



163 **164**

Enone 164. N,N‘-Dicyclohexylcarbodiimide (45.8 mg, 0.220 mmol, 2.00 equiv), anhydrous copper(I) chloride (5.5 mg, 56 µmol, 0.50 equiv) and *β*-hydroxy ketone **163** (56 mg, 0.11 mmol, 1 equiv) were suspended in dichloromethane (1.11 mL) in a pressure tube. The tube was sealed and the suspension was heated to 60 °C. After 4 h, heating was ceased and the suspension was filtered through a short plug of celite. The filter cake was rinsed with ethyl acetate (10 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **164** (46 mg, 85%) as a colorless oil.

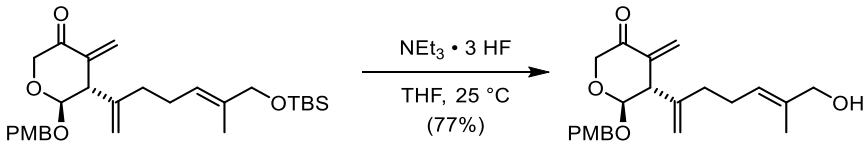
TLC (10% ethyl acetate in hexanes): R_f = 0.39 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.17–7.12 (m, 2H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.40 (t, *J* = 1.3 Hz, 1H), 5.43 (t, *J* = 6.4 Hz, 1H), 5.05 (d, *J* = 1.4 Hz, 1H), 4.96 (d, *J* = 2.7 Hz, 1H), 4.90 (s, 2H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.23 (d, *J* = 17.7 Hz, 1H), 4.09 (d, *J* = 17.7 Hz, 1H), 3.97 (s, 2H), 3.42–3.39 (m, 1H), 3.28 (s, 3H), 2.12 (dt, *J* = 11.8, 5.7 Hz, 2H), 2.05 (dt, *J* = 11.6, 5.4 Hz, 2H), 1.55 (s, 3H), 1.00 (s, 9H), 0.07 (s, 6H). **^{13}C NMR** (101 MHz, C_6D_6) δ 195.2, 160.0, 147.9, 140.9, 135.3, 129.8, 129.6, 125.5, 123.9, 114.2, 113.8, 98.3, 69.3, 68.8, 67.6, 54.8, 52.7, 34.3, 26.2, 26.0, 18.6, 13.6, −5.1.

HR-MS (ESI): calcd for $(C_{28}H_{46}O_5NSi)^+$ $(M+NH_4)^+$: 504.3145, found: 504.3141.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2856, 1706, 1613, 1514, 1463, 1250, 1169, 1112, 1068, 1035 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +46.0 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



164 **165**

Allyl alcohol 165. Triethylamine trihydrofluoride (0.12 mL, 0.71 mmol, 7.5 equiv) was added dropwise to a solution of enone **164** (46 mg, 95 µmol, 1 equiv) in tetrahydrofuran (1 mL). After 15 h, saturated aqueous sodium bicarbonate solution (10 mL) was carefully added, followed by ethyl acetate (10 mL). Solid sodium bicarbonate was added until no further gas evolution was observed. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **165** (27 mg, 77%) as a colorless oil.

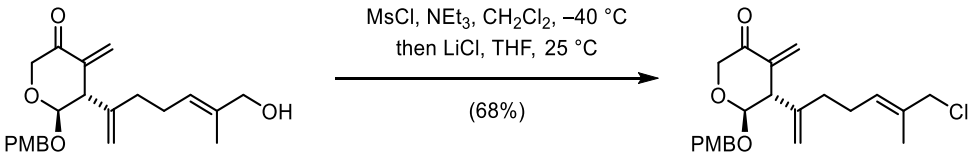
TLC (50% ethyl acetate in hexanes): R_f = 0.29 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.16–7.12 (m, 2H), 6.78–6.73 (m, 2H), 6.39 (s, 1H), 5.29–5.19 (m, 1H), 5.06–5.02 (m, 1H), 4.96 (d, *J* = 2.8 Hz, 1H), 4.89 (s, 2H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.23 (d, *J* = 17.7 Hz, 1H), 4.09 (d, *J* = 17.7 Hz, 1H), 3.75 (s, 2H), 3.40 (br s, 1H), 3.27 (s, 3H), 2.10–1.96 (m, 4H), 1.49 (s, 3H), 0.88 (br s, 1H). **^{13}C NMR** (101 MHz, C_6D_6) δ 195.3, 160.0, 147.9, 140.8, 135.9, 129.9, 129.5, 125.6, 124.4, 114.2, 113.8, 98.1, 69.2, 68.5, 67.6, 54.8, 52.8, 34.1, 26.1, 13.7.

HR-MS (ESI): calcd for ($C_{22}H_{32}O_5N$) $(M+NH_4)^+$: 390.2280, found: 390.2277.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3426, 2916, 1703, 1612, 1514, 1457, 1424, 1389, 1303, 1249, 1171, 1120, 1069, 1034 cm^{-1}.

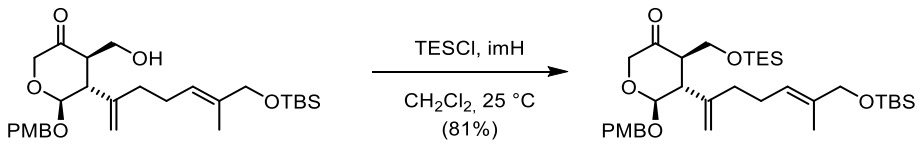
$[\boldsymbol{\alpha}]_{589}^{20}$ = +63.8 (c = 0.7 · 10 g · mL^{-1}, CH_2Cl_2).



165 **156**

Allyl chloride 156. Mesyl chloride (5.7 µL, 73 mmol, 2.6 equiv) was added dropwise to a solution of allyl alcohol **165** (10.5 mg, 28.2 µmol, 1 equiv) and triethylamine (12.5 µL, 90.2 µmol, 3.20 equiv) at –40 °C. After 1 h 10 min, the solution was transferred to a separate flask containing lithium chloride (9.6 mg, 0.22 mmol, 8.0 equiv) in tetrahydrofuran (0.3 mL) at 25 °C. After 2 h, the solution was diluted with pentane (5 mL) and water (5 mL). The layers were separated and the organic layer was washed with water (3×5 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by quick flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **156** as a colorless oil. The product was immediately used for the next step.

^{1}H NMR (200 MHz, C_6D_6) δ 7.16–7.10 (m, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.39 (s, 1H), 5.19–5.07 (m, 1H), 5.01 (s, 1H), 4.96–4.75 (m, 3H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.38–3.98 (m, 3H), 3.64 (s, 2H), 3.39–3.32 (m, 1H), 3.27 (s, 3H), 2.17–1.81 (m, 4H), 1.50 (s, 3 H).



163 **168**

TES ether 168. Chlorotriethylsilane (0.12 mL, 0.71 mmol, 1.2 equiv) was added to a solution of *β*-hydroxy ketone **163** (300 mg, 0.590 mmol, 1 equiv) and imidazole (81 mg, 1.2 mmol, 2.0 equiv) in dichloromethane (1.2 mL) at 25 °C. After 2 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **168** (299 mg, 81%) as a colorless oil.

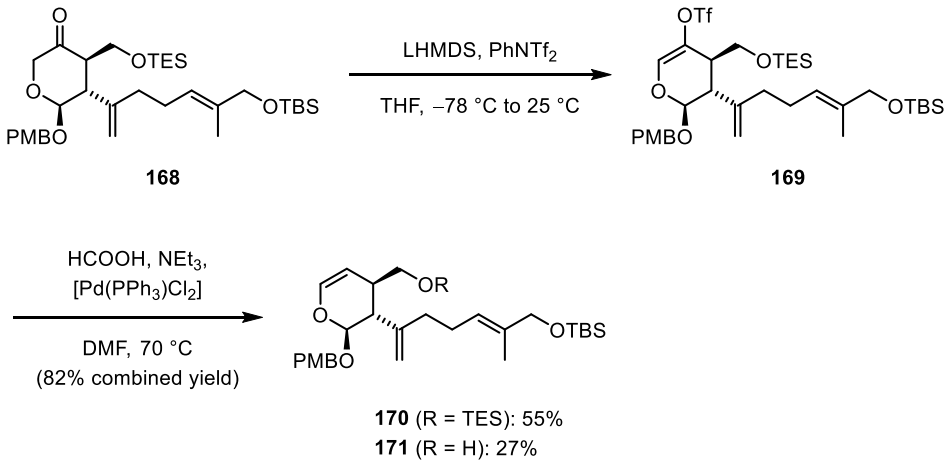
TLC (10% ethyl acetate in hexanes): R_f = 0.25 (UV, CAM).

^{1}H NMR (599 MHz, C_6D_6) δ 7.20–7.17 (m, 2H), 6.81 – 6.75 (m, 2H), 5.55–5.51 (m, 1H), 4.98 (s, 1H), 4.94 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.18 (d, *J* = 16.9 Hz, 1H), 4.15 (dd, *J* = 9.8, 2.6 Hz, 1H), 4.02 (d, *J* = 1.5 Hz, 2H), 3.79 (d, *J* = 16.9 Hz, 1H), 3.64 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.30 (s, 3H), 3.03 (dd, *J* = 12.1, 5.8 Hz, 1H), 2.36 (ddd, *J* = 12.1, 3.7, 2.7 Hz, 1H), 2.31–2.16 (m, 4H), 1.64–1.61 (m, 3H), 1.03 (t, *J* = 8.0 Hz, 9H), 1.00 (s, 9H), 0.71–0.58 (m, 6H), 0.09 (s, 6H). **^{13}C NMR** (151 MHz, C_6D_6) δ 208.0, 159.9, 148.3, 135.2, 130.1, 129.8, 124.3, 114.1, 112.0, 102.4, 69.4, 68.9, 66.9, 57.8, 54.8, 50.1, 47.0, 35.8, 26.2, 26.0, 13.6, 7.1, 4.8, −5.1.

HR-MS (ESI): calcd for ($C_{34}H_{62}O_6NSi_2$) $(M+NH_4)^+$: 636.4116, found: 636.4101.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2878, 1736, 1614, 1515, 1463, 1250, 1113, 1038 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +86.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



Vinyl triflate 169. Lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 1.78 mL; 1.78 mmol, 1.20 equiv) was added dropwise to a solution of TES ether **168** (916 mg, 1.48 mmol, 1 equiv) in tetrahydrofuran (15 mL) at –78 °C. After 45 min, a solution of *N*-phenylbis(trifluoromethanesulfonimide) (740 mg, 2.07 mmol, 1.40 equiv) in tetrahydrofuran (0.8 mL) was added dropwise. The solution was allowed to gradually warm to 25 °C over 2 h. After 30 min at 25 °C, saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (50 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column

chromatography on silica gel (3% ethyl acetate in hexanes) to afford **169** as a colorless oil, containing minor impurities. The product was used as received for the next step.

TLC (10% ethyl acetate in hexanes): R_f = 0.38 (UV, CAM).

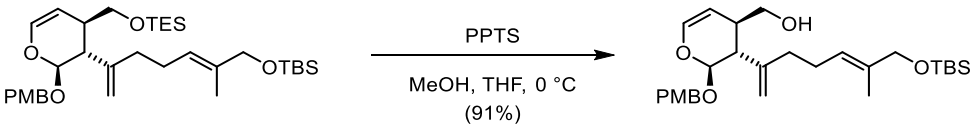
^{1}H NMR (599 MHz, C_6D_6) δ 7.15–7.11 (m, 2H), 6.81–6.74 (m, 2H), 6.62 (d, *J* = 1.6 Hz, 1H), 5.51–5.45 (m, 1H), 4.98–4.95 (m, 2H), 4.84 (d, *J* = 5.5 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.26 (d, *J* = 11.3 Hz, 1H), 3.99 (s, 2H), 3.97 (dd, *J* = 9.9, 5.9 Hz, 1H), 3.79 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.29 (s, 3H), 3.08 (app t, *J* = 5.9 Hz, 1H), 2.86 (app tdd, *J* = 5.9, 3.7, 1.6 Hz, 1H), 2.29–2.07 (m, 4H), 1.61 (s, 3H), 1.00 (s, 9H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.62–0.54 (m, 6H), 0.08 (s, 6H). **^{13}C NMR** (151 MHz, C_6D_6) δ 160.1, 147.0, 138.5, 135.4, 129.8, 129.3, 124.0, 119.2 (q, *J* = 320.8 Hz), 114.1, 112.2, 100.6, 70.8, 68.9, 60.0, 54.8, 43.9, 42.9, 36.4, 26.2, 26.0, 18.6, 13.6, 7.0, 4.7, −5.1. **^{19}F NMR** (377 MHz, C_6D_6) δ −73.84.

HR-MS (ESI): calcd for $(C_{35}H_{61}O_8NF_3SSi_2)$ $(M+NH_4)^+$: 768.3609, found: 768.3593.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2934, 2858, 1314, 1515, 1422, 1249, 1211, 1142, 1099, 1069 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +40.6 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).

Alkene 170 and 171. Formic acid (0.28 mL, 7.4 mmol, 5.0 equiv) was added dropwise to a solution of triflate **169** (1.11 g, 1.48 mmol, 1 equiv), triethylamine (1.54 mL, 11.1 mmol, 7.50 equiv) and bis(triphenylphosphine)palladium(II) chloride (46 mg, 0.065 mmol, 0.10 equiv) in *N*,*N*-dimethylformamide (14.8 mL). The yellow solution was heated to 70 °C. After 15 min, heating was ceased and the solution was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% to 25% ethyl acetate in hexanes) to afford **170** (490 mg, 55%) and **171** (198 mg, 27%) as colorless oils. TES ether **170** was directly used for the next step.



170 **171**

Alcohol 171. Pyridinium *p*-toluenesulfonate (20.4 mg, 81.3 µmol, 0.10 equiv) was added to a solution of TES ether **170** (490 mg, 0.810 mmol, 1 equiv) in a mixture of methanol and tetrahydrofuran (v/v = 5:1, 24.5 mL) at 0 °C. After 90 min, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **171** (362 mg, 91%) as a colorless oil.

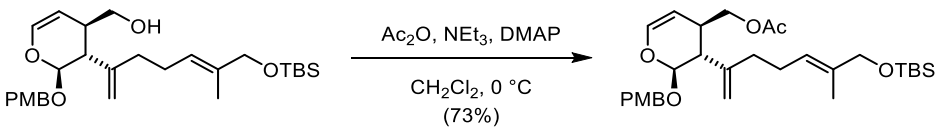
TLC (50% ethyl acetate in hexanes): R_f = 0.54 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.20 (d, *J* = 8.4 Hz, 2H), 6.80–6.73 (m, 2H), 6.36 (dd, *J* = 6.3, 2.0 Hz, 1H), 5.48 (t, *J* = 6.8 Hz, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 4.86–4.79 (m, 2H), 4.75 (dd, *J* = 6.3, 2.8 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.99 (s, 2H), 3.53 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.34 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.28 (s, 3H), 2.53 (t, *J* = 7.0 Hz, 1H), 2.30–2.09 (m, 5H), 1.59 (s, 3H), 1.36 (s, 1H), 1.00 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (100 MHz, C_6D_6) δ 159.8, 149.0, 141.7, 135.0, 130.0, 129.8, 124.6, 114.1, 110.9, 103.3, 100.3, 70.2, 69.0, 65.0, 54.7, 46.2, 39.6, 36.3, 26.2, 26.0, 18.6, 13.7, −5.1.

HR-MS (ESI): calcd for $(C_{28}H_{48}O_5NSi)^+$ $(M+NH_4)^+$: 506.3302, found: 506.3293.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3442, 2953, 2928, 2856, 1651, 1613, 1514, 1463, 1248, 1152, 1108, 1061, 1031, 1007 cm^{-1}.

$[\alpha]_{589}^{20}$ = +28.6 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



171 **172**

Acetate 172. Acetic anhydride (34 µL, 0.36 mmol, 2.6 equiv) was added dropwise to a solution of alcohol **171** (68.4 mg, 0.14 mmol, 1 equiv), triethylamine (58 µL, 0.42 mmol, 3.0 equiv) and

4-dimethylaminopyridine (1.7 mg, 14 µmol, 0.1 equiv) in dichloromethane (1.4 mL) at 0 °C. After 30 min, saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **172** (54 mg, 73%) as a colorless oil.

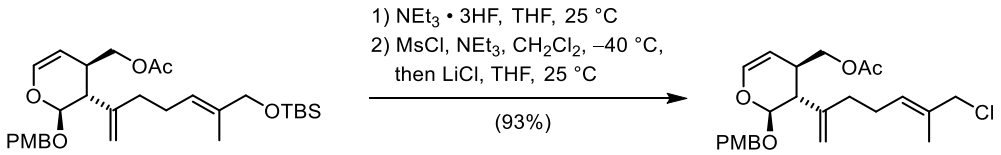
TLC (20% ethyl acetate in hexanes): R_f = 0.46 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.32 (dd, *J* = 6.2, 1.4 Hz, 1H), 5.53–5.43 (m, 1H), 4.94 (s, 1H), 4.87 (s, 1H), 4.84–4.78 (m, 2H), 4.72 (dd, *J* = 6.3, 2.1 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.31–4.24 (m, 1H), 3.99 (d, *J* = 7.8 Hz, 3H), 3.28 (s, 3H), 2.50 (d, *J* = 5.4 Hz, 2H), 2.15 (dq, *J* = 19.6, 7.3 Hz, 4H), 1.67 (s, 3H), 1.60 (s, 3H), 1.00 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (101 MHz, C_6D_6) δ 169.7, 159.5, 147.8, 141.4, 134.8, 129.6, 129.4, 124.0, 113.7, 110.8, 102.0, 100.1, 69.9, 68.5, 65.7, 54.4, 45.4, 36.0, 25.8, 25.5, 20.1, 18.2, 13.3, −5.4.

HR-MS (ESI): calcd for $(C_{30}H_{50}O_6NSi)^+$ $(M+NH_4)^+$: 548.3407, found: 548.3397.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930, 2856, 1742, 1653, 1613, 1514, 1463, 1362, 1248, 1232, 1110, 1036 cm^{-1}.

$[\alpha]_{589}^{20}$ = +9.8 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



172 **174**

Allylic alcohol 174. Triethylamine trihydrofluoride (0.11 mL, 0.68 mmol, 7.5 equiv) was added dropwise to a solution of acetate **172** (48 mg, 90 µmol, 1 equiv) in tetrahydrofuran (1 mL) at 25 °C. After 15 h, the solution was carefully diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL) and solid sodium bicarbonate was added until no further gas evolution was observed. Water (10 mL) was then added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×10 mL), the combined organic layers were washed with saturated aqueous sodium chloride (10 mL) and the washed solution was dried over sodium sulfate.

The dried solution was filtered and the filtrate was concentrated. The crude product (39 mg, quant.) was obtained as a colorless oil and was used without further purification for the next step.

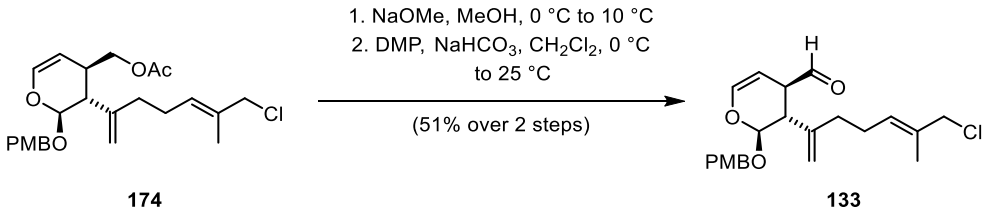
Triethylamine (42 µL, 0.30 mmol, 3.2 equiv) was added to a solution of the crude allylic alcohol (39 mg, 94 µmol, 1 equiv) in dichloromethane (0.6 mL), the solution was cooled to −40 °C and mesyl chloride (19 µL, 24 µmol, 2.6 equiv) was added dropwise. After 1 h 15 min, the solution was transferred to a suspension of anhydrous lithium chloride (24 mg, 0.56 mmol, 6.0 equiv) in tetrahydrofuran (0.6 mL) at 25 °C. Further tetrahydrofuran (0.4 mL) was added to ensure complete transfer of the mesylate. After 3 h, saturated aqueous sodium bicarbonate solution (10 mL) and diethyl ether (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude chloride **174** (38 mg, 93%) was used without further purification for the next step.

^{1}H NMR (599 MHz, C_6D_6) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.32 (dd, *J* = 6.2, 2.1 Hz, 1H), 5.22 (t, *J* = 6.5 Hz, 1H), 4.84 (s, 1H), 4.82 (s, 1H), 4.81–4.77 (m, 2H), 4.72 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.24 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.92 (dd, *J* = 10.6, 6.8 Hz, 1H), 3.69 (s, 2H), 3.29 (d, *J* = 0.7 Hz, 3H), 2.46 (dtd, *J* = 9.3, 5.4, 4.9, 2.5 Hz, 1H), 2.42 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.03–1.93 (m, 4H), 1.66 (d, *J* = 0.7 Hz, 3H), 1.54 (s, 3H). **^{13}C NMR** (151 MHz, $cdcl_3$) δ 170.0, 159.9, 147.8, 141.8, 132.3, 130.2, 129.8, 114.1, 111.3, 102.3, 100.5, 70.4, 66.0, 54.8, 52.2, 46.0, 36.6, 35.7, 26.2, 20.4, 14.1.

HR-MS (ESI): calcd for $(C_{24}H_{35}O_5NCl)^+$ $(M+NH_4)^+$: 452.2204, found: 452.2197.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2939, 1739, 1651, 1613, 1514, 1232, 1157, 1122, 1035 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +10.1 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



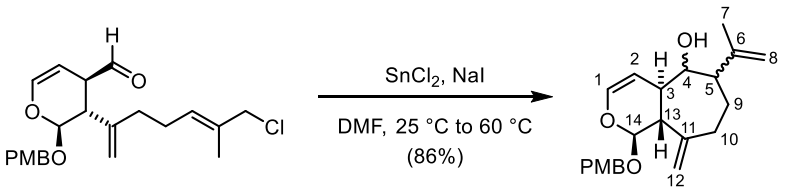
174 **133**

Aldehyde 133. Sodium methoxide (0.5 M in methanol, 0.17 mL, 85 µmol, 0.50 equiv) was added dropwise to a solution of chloride **174** (74 mg, 0.17 mmol, 1 equiv) in methanol (1.7 mL) at 0 °C. The solution was allowed to slowly warm to 10 °C over the course of 3 h 15 min. Then, saturated

aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude alcohol (67 mg, quant.) was used without further purification for the next step. The product was found to be rather unstable and had to be stored at –30 °C in the dark. Complete decomposition was observed after two days in benzene at 25 °C.

Dess–Martin periodinane (14.9 mg, 35.1 μmol, 1.50 equiv) was added to a suspension of sodium bicarbonate (12 mg, 0.14 mmol, 6.0 equiv) in HPLC-grade dichloromethane (0.4 mL) at 0 °C. A solution of the crude alcohol (9.2 mg, 23 μmol, 1 equiv) in HPLC-grade dichloromethane (0.3 mL) was added dropwise and upon completion of the addition, the suspension was allowed to warm to 25 °C. After 1 h 15 min, diethyl ether (0.5 mL) was added and the suspension was filtered through a short plug of celite. The filter cake was rinsed with diethyl ether (15 mL). The filtrate was concentrated and the crude product was purified by quick flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **133** (4.7 mg, 51%) as a colorless oil. Aldehyde **133** was found to be highly unstable and was used for the next step immediately after its preparation.

^{1}H NMR (400 MHz, C_6D_6) δ 9.42 (s, 1H), 7.16–7.11 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.20 (dd, *J* = 6.3, 1.7 Hz, 1H), 5.15 (t, *J* = 6.7 Hz, 1H), 4.93 (s, 1H), 4.85 (d, *J* = 4.0 Hz, 1H), 4.81 (s, 1H), 4.71 (dd, *J* = 6.2, 4.4 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 3.67 (s, 2H), 3.26 (s, 3H), 2.85 (t, *J* = 4.3 Hz, 1H), 2.53 (t, *J* = 4.5 Hz, 1H), 1.99–1.83 (m, 4H), 1.53 (s, 3H).



133 **176**

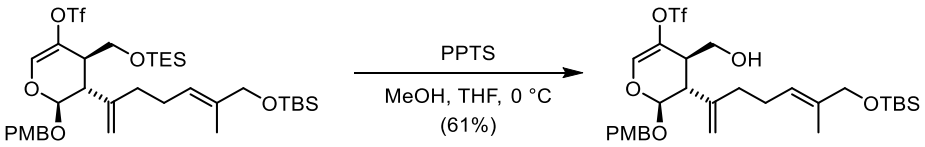
Bicycle 176. Sodium iodide (14.5 mg, 96.7 μmol, 9.00 equiv) and tin(II) chloride (9.2 mg, 48 μmol, 4.5 equiv, 99.95% purity) were added to a dry Schlenk flask and the flask was evacuated and back-filled with argon three times. Degassed dimethylformamide (0.27 mL) was added and the flask was covered with aluminum foil. The solution was stirred for 30 min at 25 °C before a solution of the aldehyde (4.2 mg, 11 μmol, 1 equiv) in degassed dimethylformamide (0.2 mL) was added. After 30 min, the solution was heated to 60 °C. After 1 h 20 min, heating was ceased and the solution

was allowed to cool to 25 °C. Half-saturated sodium bicarbonate solution (5 mL) and ethyl acetate (5 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (2×10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **176** (3.3 mg, 86%, d.r. = 3:1) as a colorless oil.

*Note: Bicycle **176** was isolated as a mixture of inseparable diastereomers (d.r. = 3:1). Only the signals for the major diastereomers are reported (assignment by 2D NMR analysis).*

^{1}H NMR (400 MHz, C_6D_6) δ 7.27 (d, *J* = 8.4 Hz, 2H, PMB), 6.80–6.73 (m, 2H, PMB), 6.50 (dd, *J* = 6.2, 1.9 Hz, 1H, H-1), 5.55 (dd, *J* = 6.2, 1.7 Hz, 1H, H-2), 5.05 (d, *J* = 8.7 Hz, 1H, H-14), 4.92 (d, *J* = 11.3 Hz, 1H, PMB), 4.90–4.85 (m, 1H, H-12a), 4.64–4.53 (m, 4H, H-12b, H-8, H-15), 3.27 (s, 3H, PMB), 3.00 (app td, *J* = 9.5, 2.5 Hz, 1H, H-4), 2.39–2.21 (m, 3H, H-9a, H-3, H-13), 2.16–1.93 (m, 2H, H-9b, H5), 1.81 (d, *J* = 2.6 Hz, 1H, OH), 1.37 (s, 3H, H-7), 1.33–1.20 (m, 2H, H-10). **^{13}C NMR** (101 MHz, C_6D_6) δ 159.9 (PMB), 150.2 (C-11), 148.2 (C-6), 141.0 (C-1), 130.2 (PMB), 130.2 (PMB), 114.0 (PMB), 112.9 (C-8), 110.4 (C-12), 105.8 (C-2), 100.5 (C-14), 76.8 (C-4), 70.7 (PMB), 54.7 (PMB), 51.7 (C-5), 49.9 (C-3), 42.3 (C-13), 36.9 (C-9), 27.2 (C-10), 18.41 (C-7).

HR-MS (ESI): calcd for $(C_{22}H_{32}O_4N)^+$ $(M+NH_4)^+$: 374.2331, found: 374.2326.



169 **177**

Alcohol 177. Pyridinium *p*-toluenesulfonate (27 mg, 0.11 mmol, 0.15 equiv) was added to a solution of triflate **169** (534 mg, 0.71 mmol, 1 equiv) in a mixture of methanol and tetrahydrofuran (v/v = 5:1, 24 mL) at 0 °C. After 4 h, saturated aqueous sodium bicarbonate solution (25 mL) and ethyl acetate (50 mL) were added and the mixture was allowed to warm to 25 °C. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (25 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% to 20% ethyl acetate in hexanes) to afford **177** (276 mg, 61%) as a colorless oil.

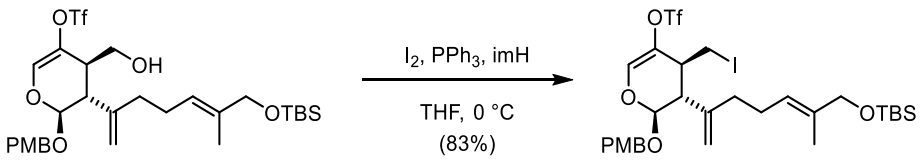
TLC (10% ethyl acetate in hexanes): R_f = 0.14 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.26–7.20 (m, 2H), 6.91–6.84 (m, 2H), 6.81 (d, *J* = 1.6 Hz, 1H), 5.39–5.32 (m, 1H), 4.99 (d, *J* = 9.4 Hz, 1H), 4.90 (dd, *J* = 4.3, 1.0 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.00–3.97 (m, 2H), 3.88 (ddd, *J* = 11.6, 6.9, 4.7 Hz, 1H), 3.80 (d, *J* = 1.0 Hz, 4H), 3.70–3.64 (m, 1H), 2.74 (t, *J* = 4.6 Hz, 1H), 2.71–2.67 (m, 1H), 2.52 (s, 1H), 2.23–2.03 (m, 4H), 1.58 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.7, 146.6, 138.3, 135.2, 134.7, 129.9, 128.3, 123.5, 118.6 (q, *J* = 320.7 Hz), 114.1, 112.5, 98.5, 70.7, 68.6, 61.2, 55.4, 46.0, 41.7, 35.7, 26.1, 25.8, 18.6, 13.6, −5.1. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −73.34.

HR-MS (ESI): calcd for $(C_{29}H_{47}O_8NF_3SSi)^+$ $(M+NH_4)^+$: 654.2744, found: 654.2739.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3444, 2955, 2931, 2887, 2857, 1614, 1515, 1419, 1248, 1208, 1140, 1064, 1035 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +53.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



177 **178**

Iodide 178. Iodine (64 mg, 0.25 mmol, 1.6 equiv) was added to a solution of triphenylphosphine (66 mg, 0.25 mmol, 1.6 equiv) and imidazole (34 mg, 0.50 mmol, 3.2 equiv) in tetrahydrofuran (1.6 mL) at 0 °C. After 15 min, a solution of alcohol **177** (100 mg, 0.160 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added dropwise. After 1 h, aqueous sodium thiosulfate solution (0.1 M, 10 mL) and ethyl acetate (10 mL) were added and the mixture was allowed to warm to 25 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **178** as a colorless oil.

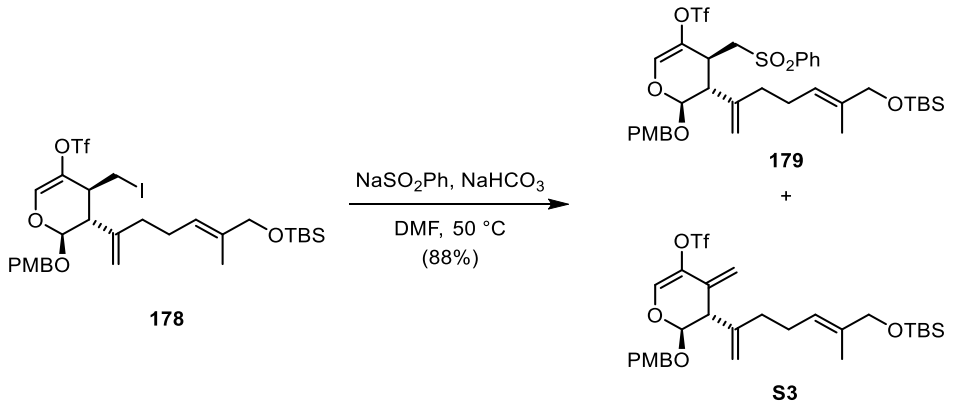
TLC (10% ethyl acetate in hexanes): R_f = 0.36 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H), 6.90–6.86 (m, 2H), 6.81 (d, *J* = 1.4 Hz, 1H), 5.39–5.32 (m, 1H), 5.00 (s, 1H), 4.97–4.91 (m, 2H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 3.99 (s, 2H), 3.81 (s, 3H), 3.50 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.36 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.77 (t, *J* = 5.6 Hz, 1H), 2.61–2.54 (m, 1H), 2.29–2.15 (m, 2H), 2.14–2.00 (m, 2H), 1.60 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6, 145.4, 138.4, 135.3, 134.4, 129.6, 128.6, 123.4, 118.6 (q, *J* = 320.9 Hz), 114.0, 113.0, 99.6, 70.8, 68.6, 55.4, 47.5, 40.4, 35.3, 26.1, 25.8, 18.6, 13.7, 7.4, −5.1.

HR-MS (ESI): calcd for $(C_{29}H_{46}O_7NF_3ISSi)^+$ $(M+NH_4)^+$: 764.1761, found: 764.1751.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2930, 2857, 1314, 1515, 1464, 1422, 1249, 1212, 1140, 1098, 1069 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +32.0 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



Sulfone 179. Sodium benzenesulfinate (33 mg, 0.20 mmol, 1.5 equiv) was added to a suspension of iodide **178** (100 mg, 0.130 mmol, 1 equiv) and sodium bicarbonate (12 mg, 0.15 mmol, 1.1 equiv) in dimethylformamide (1.3 mL). The suspension was heated to 50 °C. After 15 h, heating was ceased, water (10 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **179** (37 mg, 36%) and **S3** (43 mg, 52%) as colorless oils.

179:

TLC (10% ethyl acetate in hexanes): R_f = 0.12 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.86–7.81 (m, 2H), 7.68–7.63 (m, 1H), 7.58–7.51 (m, 2H), 7.25–7.21 (m, 2H), 6.91–6.88 (m, 2H), 6.65 (d, *J* = 1.2 Hz, 1H), 5.41–5.36 (m, 1H), 5.03 (d, *J* = 1.1 Hz, 1H), 5.01 (s, 1H), 4.95 (s, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.06–3.99 (m, 3H), 3.83 (s, 3H), 3.38 (d, *J* = 1.4 Hz, 1H), 3.25 (dd, *J* = 14.7, 1.9 Hz, 1H), 2.91 (d, *J* = 10.9 Hz, 1H), 2.27–2.19 (m, 2H), 2.19–2.05 (m, 2H), 1.61 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.6, 145.7, 138.9, 137.4, 135.3, 134.0, 133.5, 129.6, 129.6, 129.6, 128.7, 128.1, 123.5, 118.4 (q, *J* = 320.7 Hz), 114.1, 112.4, 97.7, 70.4, 68.7, 55.4, 54.7, 44.2, 35.7, 33.4, 26.1, 26.0, 18.6, 13.7, −5.1. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −73.35.

HR-MS (ESI): calcd for $(C_{35}H_{51}O_9NF_3S_2Si)^+$ $(M+NH_4)^+$: 778.2727, found: 778.2706.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2931, 2857, 1614, 1515, 1423, 1249, 1213, 1174, 1140, 1109, 1070 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +58.0 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).

S3:

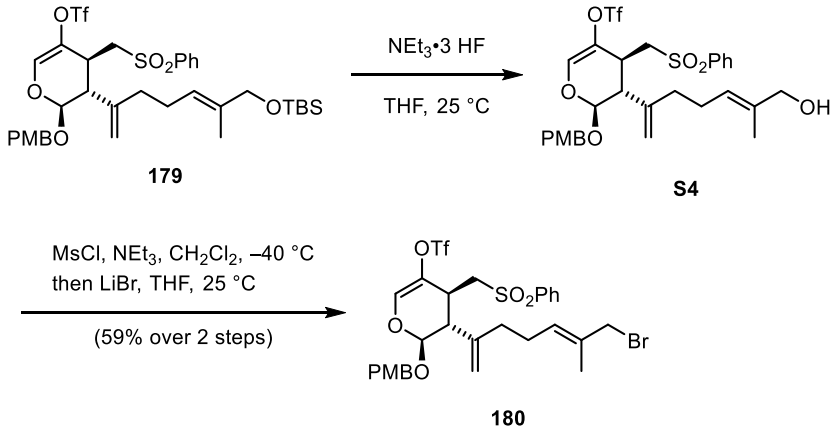
TLC (10% ethyl acetate in hexanes): R_f = 0.33 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.26–7.22 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 0.9 Hz, 1H), 5.34 (tq, *J* = 7.0, 1.4 Hz, 1H), 5.31 (s, 1H), 5.07 (d, *J* = 3.3 Hz, 1H), 4.99 (t, *J* = 0.9 Hz, 1H), 4.99–4.95 (m, 1H), 4.95 (t, *J* = 1.5 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.01–3.97 (m, 2H), 3.80 (s, 3H), 3.23 (dd, *J* = 3.4, 1.2 Hz, 1H), 2.19–2.12 (m, 2H), 2.12–1.96 (m, 2H), 1.57 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6, 144.8, 136.6, 135.2, 134.7, 132.2, 129.8, 128.6, 123.4, 118.7 (q, *J* = 320.5 Hz), 114.0, 113.3, 110.7, 99.1, 70.2, 68.5, 55.4, 50.7, 34.1, 26.1, 25.7, 18.6, 13.6, −5.1. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −73.54.

HR-MS (ESI): calcd for $(C_{29}H_{45}O_7NF_3SSi)^+$ $(M+NH_4)^+$: 636.2838, found: 636.2626.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2931, 2896, 2857, 1654, 1614, 1464, 1422, 1303, 1248, 1209, 1141, 1081, 1061, 1110 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +68.7 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



Bromide 180. Triethylamine trihydrofluoride (41 µL, 0.25 mmol, 7.0 equiv) was added to a solution of sulfone **179** (27 mg, 36 µmol, 1 equiv) in tetrahydrofuran (0.6 mL) a 25 °C. After 24 h, the solution was carefully diluted with saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate (5 mL). Solid sodium bicarbonate was then added until no further gas evolution was observed. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution as dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product **S4** was used without further purification for the next step.

Triethylamine (19 µL, 0.14 mmol, 3.8 equiv) was added to a solution of the crude allylic alcohol **S4** (assumed: 23 mg, 36 µmol, 1 equiv) in dichloromethane (0.3 mL) and the solution was cooled to –40 °C. Methanesulfonyl chloride (6.4 µL, 83 µmol, 2.3 equiv) was added dropwise. After 2 h, the solution was transferred to a flask containing anhydrous lithium bromide (47 mg, 0.54 mmol, 15 equiv) in tetrahydrofuran (0.3 mL) at 23 °C. Tetrahydrofuran (2×0.2 mL) was used to assure complete transfer. After 45 min, aqueous pH 7 buffer solution (10 mL) and diethyl ether (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **180** (15.1 mg, 59%) as a slightly yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.45 (UV, CAM).

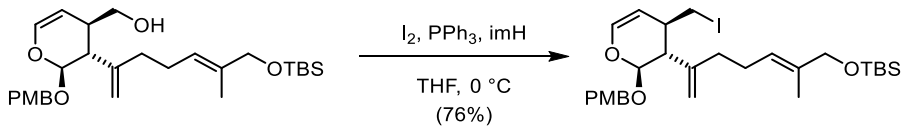
^{1}H NMR (599 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.69–7.64 (m, 1H), 7.59–7.53 (m, 2H), 7.26–7.21 (m, 2H), 6.93–6.88 (m, 2H), 6.67 (d, *J* = 1.1 Hz, 1H), 5.59 (t, *J* = 6.3 Hz, 1H), 5.06–5.02 (m, 2H), 4.96–4.93 (m, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.02 (dd, *J* = 14.6,

10.5 Hz, 1H), 3.97 (s, 2H), 3.83 (s, 3H), 3.40–3.38 (m, 1H), 3.24 (dd, *J* = 14.6, 1.9 Hz, 1H), 2.93 (d, *J* = 10.5 Hz, 1H), 2.30–2.06 (m, 4H), 1.77 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.7, 145.2, 139.0, 137.5, 134.1, 133.3, 132.9, 130.4, 129.6, 128.6, 128.0, 118.4 (q, *J* = 320.9 Hz), 114.1, 112.7, 97.6, 70.4, 55.5, 54.7, 44.1, 41.7, 35.1, 33.3, 26.7, 14.9. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −73.29.

HR-MS (ESI): calcd for $(C_{35}H_{51}O_6NF_3SSi)^+$ $(M+NH_4)^+$: 698.3158, found: 698.3154.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1613, 1515, 1422, 1306, 1248, 1213, 1175, 1140, 1110, 1071, 1034 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +63.0 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



171 **182**

Iodide 182. Iodine (21 mg, 83 µmol, 1.5 equiv) was added to a solution of imidazole (11 mg, 0.17 mmol, 3.0 equiv) and triphenylphosphine (21.7 mg, 82.9 µmol, 1.50 equiv) in tetrahydrofuran (0.55 mL) at 0 °C. After 10 min, a solution of alcohol **171** (27 mg, 55 µmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added dropwise. After 2 h, aqueous sodium thiosulfate solution (0.1 M, 10 mL) was added, followed by ethyl acetate (10 mL) and the biphasic mixture was allowed to warm to 25 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **182** (25 mg, 76%) as colorless oil.

TLC (25% ethyl acetate in hexanes): R_f = 0.60 (UV, CAM).

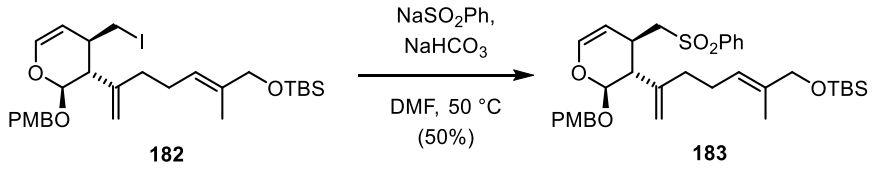
^{1}H NMR (400 MHz, C_6D_6) δ 7.18 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.27 (dd, *J* = 6.2, 1.9 Hz, 1H), 5.52–5.43 (m, 1H), 4.90 (s, 1H), 4.85 (s, 1H), 4.80 (d, *J* = 6.1 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.59 (dd, *J* = 6.3, 3.0 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.00 (s, 2H), 3.28 (s, 3H), 3.21 (dd, *J* = 9.5, 5.7 Hz, 1H), 2.90 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.55 (t, *J* = 6.6 Hz, 1H), 2.27–2.16 (m, 2H), 2.15–2.03 (m, 3H), 1.61 (s, 3H), 1.01 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (101 MHz, C_6D_6) δ 159.8, 147.7,

141.7, 135.2, 129.9, 129.7, 124.3, 114.1, 111.4, 104.6, 99.9, 70.2, 68.9, 54.7, 48.7, 37.9, 36.1, 26.2, 26.1, 18.6, 13.7, −5.0.

HR-MS (ESI): calcd for $(C_{28}H_{47}IO_4NSi)^+$ $(M+NH_4)^+$: 616.2319, found: 616.2309.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2927, 2855, 1652, 1614, 1515, 1464, 1395, 1250, 1180, 1108, 1038 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +11.8 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



Sulfone 183. Sodium benzenesulfinate (38 mg, 0.23 mmol, 1.5 equiv) and sodium bicarbonate (14.1 mg, 0.17 mmol, 1.10 equiv) were added to a solution of iodide **182** (91.6 mg, 0.15 mmol, 1 equiv) in dimethylformamide (1.5 mL), the flask was covered with aluminum foil and the solution was heated to 50 °C. After 16 h, heating was ceased and the solution was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **183** (46.7 mg, 50%) as a colorless oil.

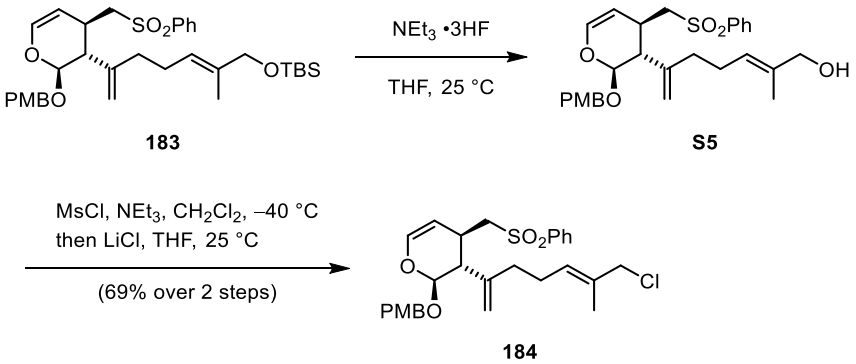
TLC (20% ethyl acetate in hexanes): R_f = 0.32 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.81–7.74 (m, 2H), 7.16–7.13 (m, 2H), 6.97–6.93 (m, 1H), 6.90 (dd, *J* = 8.3, 6.7 Hz, 2H), 6.78–6.73 (m, 2H), 6.21 (dd, *J* = 6.3, 1.8 Hz, 1H), 5.46–5.39 (m, 1H), 5.14 (dd, *J* = 6.3, 3.1 Hz, 1H), 4.84 (s, 1H), 4.81–4.75 (m, 2H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.4 Hz, 1H), 4.00 (s, 2H), 3.40 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.29 (s, 3H), 2.87 (d, *J* = 8.8 Hz, 1H), 2.82 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.52 (t, *J* = 6.3 Hz, 1H), 2.18–2.07 (m, 2H), 2.05–1.92 (m, *J* = 6.9 Hz, 2H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.01 (d, *J* = 0.6 Hz, 9H), 0.12–0.07 (m, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.9, 147.0, 141.1, 140.9, 135.3, 133.1, 129.8, 129.7, 129.1, 128.4, 124.3, 114.1, 112.1, 103.2, 99.7, 70.2, 68.9, 59.3, 54.8, 47.9, 35.6, 30.7, 26.2, 26.0, 18.6, 13.7, -5.0.

HR-MS (ESI): calcd for $(C_{34}H_{52}O_6NSSi)^+$ $(M+NH_4)^+$: 630.3285, found: 630.3270.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928, 2856, 1651, 1614, 1514, 1463, 1447, 1305, 1250, 1149, 1106, 1036 cm^{-1}.

$[\alpha]_{589}^{20}$ = +16.3 (c = 0.8 · 10 g · mL^{-1}, CH_2Cl_2).



Chloride 184. Triethylamine trihydrofluoride (50 µL, 0.31 mmol, 7.0 equiv) was added to a solution of sulfone **183** (27 mg, 44 µmol, 1 equiv) in tetrahydrofuran (0.45 mL) at 25 °C. After 16 h, the solution was carefully diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **S5** was used without further purification for the next step.

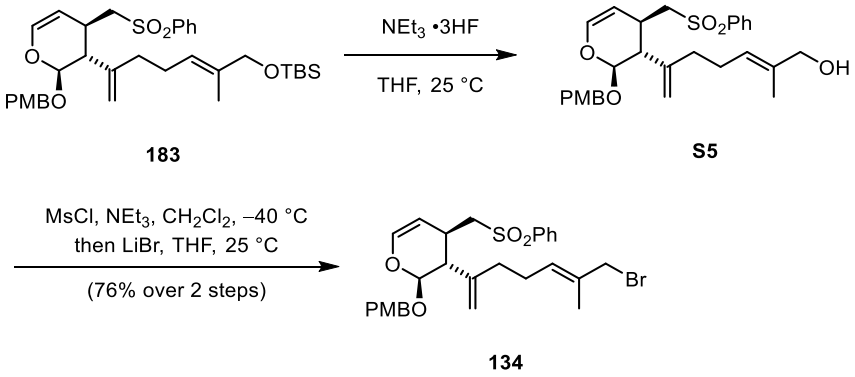
Triethylamine (20 µL, 0.14 mmol, 3.2 equiv) was added to a solution of the crude allylic alcohol **S5** (assumed: 22 mg, 44 µmol, 1 equiv) in dichloromethane (0.3 mL) and the solution was cooled to –40 °C. Methanesulfonyl chloride (8.9 µL, 0.11 µmol, 2.6 equiv) was added dropwise. After 1 h 45 min, the solution was transferred to a flask containing anhydrous lithium chloride (11 mg, 0.26 mmol, 6.00 equiv) in tetrahydrofuran (0.3 mL) at 23 °C. Tetrahydrofuran (2×0.2 mL) was used to assure complete transfer. After 1 h 30 min, aqueous pH 7 buffer solution (10 mL) and diethyl ether (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **184** (15.8 mg, 69%) as a slightly yellow oil.

^{1}H NMR (599 MHz, C_6D_6) δ 7.78–7.74 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 3H), 6.97–6.91 (m, 1H), 6.88 (ddd, *J* = 8.2, 6.6, 1.2 Hz, 2H), 6.77–6.73 (m, 2H), 6.21 (dt, *J* = 6.3, 1.5 Hz, 1H), 5.21–5.15 (m, 1H), 5.11 (ddd, *J* = 6.3, 3.2, 1.1 Hz, 1H), 4.79–4.75 (m, 3H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 3.69 (s, 2H), 3.37 (ddd, *J* = 13.9, 4.4, 0.9 Hz, 1H), 3.28 (s, 2H), 2.92–2.85 (m, 1H), 2.78 (ddd, *J* = 13.9, 8.4, 0.9 Hz, 1H), 2.51 (t, *J* = 6.4 Hz, 1H), 1.98–1.92 (m, 2H), 1.89–1.78 (m, 2H), 1.55–1.52 (m, 3H). **^{13}C NMR** (151 MHz, C_6D_6) δ 159.9, 146.6, 141.1, 141.0, 133.1, 132.3, 130.1, 129.8, 129.2, 128.0, 114.1, 112.3, 103.1, 99.4, 70.2, 59.3, 54.8, 52.2, 47.9, 34.7, 30.5, 26.2, 14.2.

HR-MS (ESI): calcd for $(C_{28}H_{37}ClO_5NS)^+$ $(M+NH_4)^+$: 534.2081, found: 534.2072.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2921, 1650, 1613, 1514, 1447, 1304, 1249, 1149, 1034 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +19.6 (c = 0.8 · 10 g · mL^{-1}, CH_2Cl_2).



183 **S5** **134**

Bromide 134. Triethylamine trihydrofluoride (50 µL, 0.31 mmol, 7.0 equiv) was added to a solution of sulfone **183** (26.7 mg, 43.6 µmol, 1 equiv) in tetrahydrofuran (0.45 mL) at 25 °C. After 16 h, the solution was carefully diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **S5** was used without further purification for the next step.

Triethylamine (18 µL, 0.13 mmol, 3.0 equiv) was added to a solution of the crude allylic alcohol **S5** (assumed: 21.7 mg, 43.6 µmol, 1 equiv) in dichloromethane (0.3 mL) and the solution was cooled to –40 °C. Methanesulfonyl chloride (6.8 µL, 87 µmol, 2.0 equiv) was added dropwise. After 1 h 45 min, the solution was transferred to a flask containing anhydrous lithium bromide (38 mg, 0.44 mmol, 10 equiv) in tetrahydrofuran (0.3 mL) at 23 °C. Tetrahydrofuran (2×0.2 mL)

was used to assure complete transfer. After 45 min, aqueous pH 7 buffer solution (10 mL) and diethyl ether (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **134** (18.5 mg, 76%) as a slightly yellow oil.

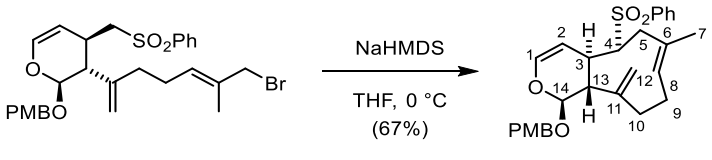
TLC (25% ethyl acetate in hexanes): R_f = 0.29 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.88–7.83 (m, 2H), 7.67–7.63 (m, 1H), 7.58–7.52 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.88–6.83 (m, 2H), 6.28 (dd, *J* = 6.3, 1.9 Hz, 1H), 5.45 (t, *J* = 7.0 Hz, 1H), 4.97 (dd, *J* = 6.3, 3.3 Hz, 1H), 4.85 (s, 1H), 4.82–4.79 (m, 2H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.93 (s, 2H), 3.81 (s, 3H), 3.41 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.03 (dd, *J* = 14.1, 8.6 Hz, 1H), 2.73–2.67 (m, 1H), 2.39 (t, *J* = 6.1 Hz, 1H), 2.16–2.04 (m, 2H), 1.93–1.88 (m, 2H), 1.73–1.71 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.5, 146.0, 141.0, 139.7, 133.8, 132.6, 130.6, 129.7, 129.4, 129.3, 128.1, 113.9, 112.5, 102.6, 98.8, 70.0, 59.4, 55.4, 47.8, 41.6, 34.3, 30.1, 26.3, 14.9.

HR-MS (ESI): calcd for $(C_{28}H_{37}O_5NBrS)^+$ $(M+NH_4)^+$: 578.1576, found: 578.1569.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3066, 2921, 1650, 1613, 1586, 1514, 1447, 1304, 1248, 1149, 1136, 1033 cm^{-1}.

$[\alpha]_{589}^{20}$ = +16.6 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



134 **185**

Bicycle 185. A solution of bromide **134** (28 mg, 50 μmol, 1 equiv) in tetrahydrofuran (1 mL) was added dropwise via syringe pump (addition rate: 1.1 mL/h) to a solution of sodium bis(trimethylsilylamide) (1.0 M in tetrahydrofuran, 0.2 mL, 0.2 mmol, 4 equiv) in tetrahydrofuran (4 mL) at 0 °C. Upon completion of the addition, stirring at 0 °C was continued for 15 min. Saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The

combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **185** (16 mg, 67%) as a colorless oil.

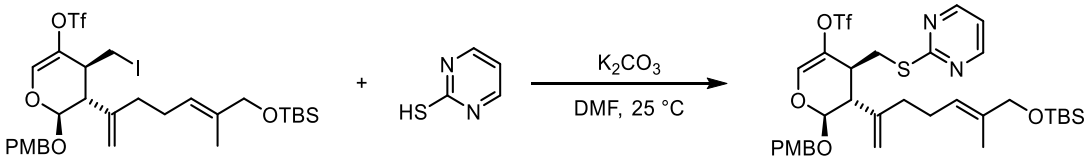
TLC (25% ethyl acetate in hexanes): R_f = 0.29 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, ^3J = 7.6 Hz, 2H, Ph), 7.53 (t, ^3J = 7.3 Hz, 1H, Ph), 7.34 (t, ^3J = 7.7 Hz, 2H, Ph), 7.27 (d, ^3J = 9.0 Hz, 2H, PMB), 6.93 (d, ^3J = 8.5 Hz, 2H, PMB), 6.01 (dd, $^3J_{1/2}$ = 6.7 Hz, $^4J_{1/3}$ = 2.2 Hz, 1H, H-1), 5.54 (t, $^3J_{8/9}$ = 7.7 Hz, 1H, H-8), 5.23 (t, $^3J_{2/1}$ = 5.7 Hz, 1H, H-2), 4.97 (s, 1H, H-12a), 4.88 (s, 1H, H-12b), 4.68 (s, 1H, H-14), 4.46 (d, $^2J_{Ha/Hb}$ = 11.8 Hz, 1H, PMB), 4.24 (d, $^2J_{Hb/Ha}$ = 11.8 Hz, 1H, PMB), 3.84 (s, 3H, PMB), 3.81–3.73 (m, 1H, H-4), 2.62–2.38 (m, 4H, H-5, H-3, H-9a), 2.30–2.21 (m, 1H, H-10a), 2.20–2.09 (m, 2H, H-9b, H-10b), 1.90 (s, 1H, H-13), 1.68 (s, 3H, H-7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3 (PMB), 149.7 (C-11), 141.1 (Ph), 139.0 (C-1), 133.0 (Ph), 131.5 (C-6), 130.0 (PMB), 129.0 (PMB), 128.7 (Ph), 128.4 (C-8), 128.0 (Ph), 113.9 (C-12, PMB), 113.9 (C-12, PMB), 103.0 (C-2), 96.1 (C-14), 68.7 (PMB), 63.3 (C-4), 55.5 (PMB), 48.3 (C-13), 39.8 (C-5), 36.8 (C-3), 35.7 (C-10), 25.5 (C-9), 17.6 (C-7).

HR-MS (ESI): calcd for $(C_{28}H_{36}O_5NS)^+$ $(M+NH_4)^+$: 498.2314, found: 498.2309.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3070, 2932, 2863, 2360, 1661, 1613, 1514, 1445, 1302, 1244, 1143, 1104, 1057, 1034 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +67.6 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



178 **205**

Sulfide 205. Potassium carbonate (10.4 mg, 75.3 µmol, 1.25 equiv) was added to a solution of 2-mercapto pyrimidine (7.6 mg, 66 µmol, 1.1 equiv) in dimethylformamide (0.3 mL) at 25 °C. After 15 min, a solution of iodide **178** (45 mg, 60 µmol, 1 equiv) in dimethylformamide (0.4 mL) was added dropwise. After 18 h, water (10 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed

solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **205** (34 mg, 77%) as a colorless oil.

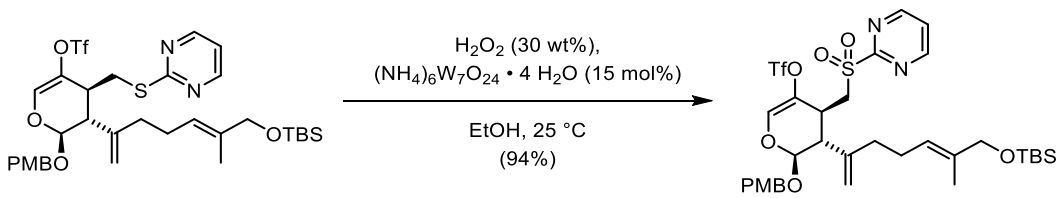
TLC (10% ethyl acetate in hexane): R_f = 0.42 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 2H), 7.26–7.20 (m, 2H), 6.96 (t, *J* = 4.8 Hz, 1H), 6.92–6.86 (m, 2H), 6.72 (d, *J* = 1.2 Hz, 1H), 5.24 (tq, *J* = 7.0, 1.4 Hz, 1H), 5.03 (d, *J* = 1.7 Hz, 1H), 4.98 (s, 1H), 4.88 (s, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 3.94 (s, 2H), 3.86–3.78 (m, 4H), 3.34 (dd, *J* = 13.9, 9.9 Hz, 1H), 3.02–2.93 (m, 2H), 2.15–2.06 (m, 2H), 2.01–1.91 (m, 2H), 1.51 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6, 159.5, 157.5, 146.3, 137.1, 136.4, 135.1, 129.5, 129.0, 123.6, 116.9, 114.1, 112.0, 98.4, 70.3, 68.7, 55.4, 44.7, 38.0, 35.7, 31.9, 26.1, 25.8, 18.6, 13.6, −5.1; (signals for CF_3 group not visible). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −73.36.

HR-MS (ESI): calcd for $(C_{33}H_{46}O_7N_2F_3S_2Si)^+$ $(M+H)^+$: 731.2468, found: 731.2451.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930, 2856, 1614, 1565, 1549, 1515, 1421, 1382, 1248, 1208, 1174, 1141, 1111, 1066, 1037 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +103.0 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).



205 **206**

Sulfone 206. Hydrogen peroxide (30 wt% in water, 16 µL, 0.15 mmol, 8.00 equiv) was added dropwise to a solution of sulfide **206** (14 mg, 19 µmol, 1 equiv) and ammonium molybdate tetrahydrate (3.6 mg, 2.9 µmol, 0.15 equiv) in ethanol (0.7 mL) at 0 °C. Upon completion of the addition, the solution was allowed to warm to 25 °C. After 4 days, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL) and aqueous sodium thiosulfate solution (0.1 M, 10 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and crude **206** (13.8 mg, 94%) was used as received.

TLC (30% ethyl acetate in hexanes): R_f = 0.44 (UV, CAM).

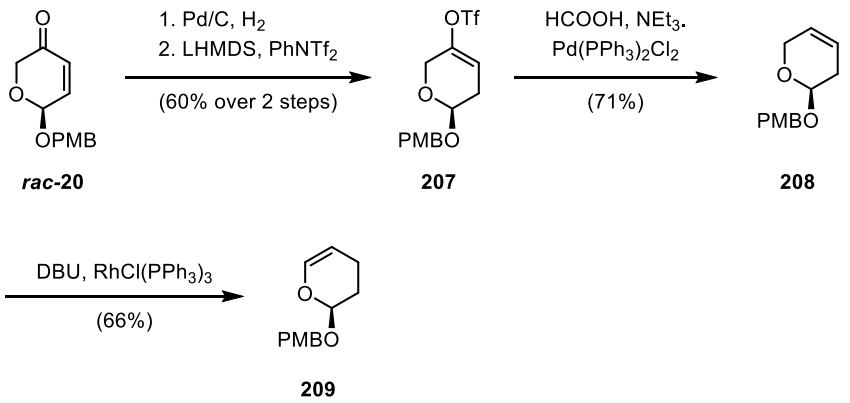
^{1}H NMR (599 MHz, $CDCl_3$) δ 8.94 (d, *J* = 4.9 Hz, 2H), 7.55 (t, *J* = 4.9 Hz, 1H), 7.26–7.23 (m, 2H), 6.92–6.87 (m, 2H), 6.70 (d, *J* = 1.1 Hz, 1H), 5.33–5.29 (m, 1H), 5.05 (d, *J* = 1.3 Hz, 1H), 5.02 (s, 1H), 4.90 (s, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.23–4.10 (m, 2H), 3.96 (s, 2H), 3.82 (s, 3H), 3.40 (s, 1H), 3.18 (d, *J* = 9.6 Hz, 1H), 2.20–2.00 (m, 4H), 1.55 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.69, 159.66, 158.98, 145.77, 137.45, 137.44, 135.04, 134.13, 129.68, 128.52, 124.01, 123.74, 118.6 (q, *J* = 321.5 Hz), 114.16, 112.20, 97.59, 70.30, 68.72, 55.43, 50.06, 44.65, 35.60, 33.83, 26.11, 26.09, 25.83, 18.57, 13.60, −5.12. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −72.86.

HR-MS (ESI): calcd for $(C_{33}H_{49}O_9N_3F_3S_2Si)^+$ $(M+NH_4)^+$: 780.2632, found: 780.2627.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2930, 2857, 1566, 1515, 1421, 1387, 1330, 1248, 1212, 1174, 1140, 1128, 1068 cm^{-1}.

$[\boldsymbol{\alpha}]_{589}^{20}$ = +61.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).

Model substrate synthesis for the introduction of the side chain:



***rac*-20** **207** **208** **209**

Triflate 207. Sodium bicarbonate (897 mg, 10.7 mmol, 5.00 equiv) and palladium on activated charcoal (10 wt%, 227 mg, 0.210 mmol, 0.100 equiv) were added to a solution of enone ***rac*-20** (500 mg, 2.13 mmol, 1 equiv) in tetrahydrofuran (21 mL) at 25 °C. The suspension was purged with hydrogen gas (1 atm) through a stainless steel needle for 1 min. Stirring of the suspension was then continued under a hydrogen atmosphere (1 atm, balloon) at 25 °C. After 1.5 h, hydrogen gas was released from the flask, the suspension was purged with argon and the mixture was filtered

through a short pad of celite. The filter cake was rinsed with diethyl ether (100 mL). The filtrate was concentrated to afford a yellow oil, which was used without further purification for the next step.

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 3.25 mL, 3.25 mmol, 1.20 equiv) was added dropwise to a solution of the crude ketone (640 mg, 2.71 mmol, 1 equiv) in tetrahydrofuran (27 mL) at –78 °C. After 45 min, a solution of *N*-phenylbis(trifluoromethansulfonimide) (1.36 g, 3.79 mmol, 1.40 equiv) in tetrahydrofuran (5 mL) was added dropwise. The solution was then allowed to warm to 25 °C over 1.5 h. After 30 min at 25 °C, saturated aqueous sodium bicarbonate solution (10 mL) was added, followed by ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% to 10% ethyl acetate in hexanes) to afford vinyl triflate **207** (601 mg, 60%) as a colorless oil.

Alkene 208. Formic acid (0.31 mL, 8.2 mmol, 5.0 equiv) was added dropwise to a solution of triflate **207** (601 mg, 1.63 mmol, 1 equiv), triethylamine (1.70 mL, 12.2 mmol, 7.50 equiv) and bis(triphenylphosphine)palladium(II) chloride (115 mg, 0.160 mmol, 0.100 equiv) in dimethylformamide (16 mL) at 0 °C. After 5 min, the solution was heated to 70 °C. When the solution turned dark brown (approximately after 15 min), heating was ceased and the solution was cooled to 25 °C. The solution was diluted with water (25 mL) and ethyl acetate (25 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **208** (254 mg, 71%) as a yellow oil.

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 6.91–6.86 (m, 2H), 5.76–5.69 (m, 2H), 4.91 (t, *J* = 3.8 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.33–4.25 (m, 1H), 4.16–4.09 (m, 1H), 3.80 (s, 3H), 2.41–2.33 (m, 1H), 2.18–2.11 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.4, 130.1, 129.8, 125.4, 121.8, 114.0, 95.4, 69.0, 61.0, 55.4, 30.4.

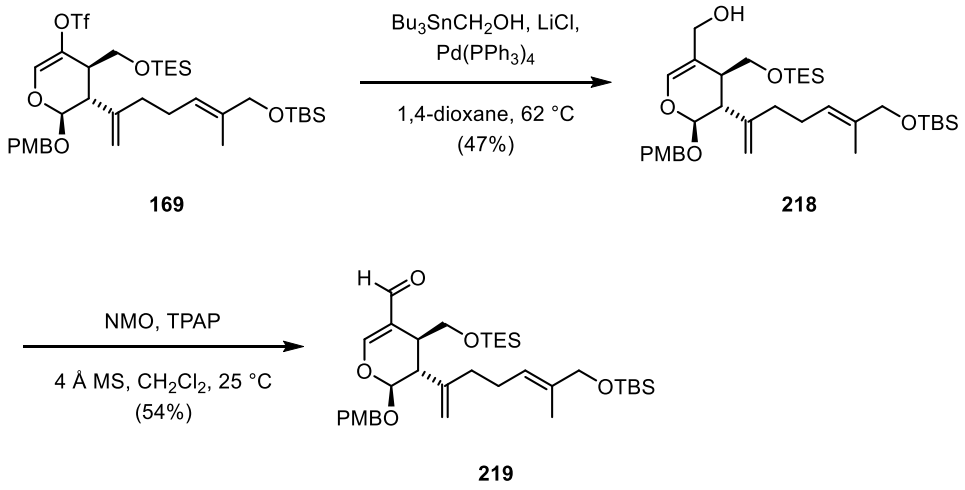
HR-MS (EI): calcd for $(C_{13}H_{16}O_3)^+$: 220.1099, found: 220.1093.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3040, 2935, 2839, 1613, 1514, 1431, 1380, 1247, 1209, 1181, 1144, 1110, 1029 cm^{-1}.

Enol ether 209. To a solution of alkene **208** (250 mg, 1.13 mmol, 1 equiv) in ethanol (14 mL) were added tris(triphenylphosphine)rhodium(I) chloride (52.5 mg, 56.7 µmol, 0.050 equiv) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.51 mL, 3.40 mmol, 3.00 equiv). The solution was heated to 80 °C. After 20 h, heating was ceased and the solution was concentrated. The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford **209** (166 mg, 66%) as a colorless oil.

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 6.92–6.85 (m, 2H), 6.29–6.25 (m, 1H), 5.07–5.03 (m, 1H), 4.81–4.76 (m, 2H), 4.55 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 2.23–2.13 (m, 1H), 1.97–1.79 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.3, 140.6, 130.1, 129.6, 113.9, 101.9, 95.7, 69.2, 55.4, 26.8, 16.3.

HR-MS (EI): calcd for $(C_{13}H_{16}O_3)^+$: 220.1099, found: 220.1097.



169 **218** **219**

Aldehyde 219. Lithium chloride (5.6 mg, 0.13 mmol, 2.0 equiv) was placed in a Schlenk flask and the flask was heated with a heat gun while being evacuated. The flask was then allowed to cool to 25 °C and was purged with argon. This procedure was repeated two times. Tetrakis(triphenylphosphine)palladium (7.6 mg, 6.7 µmol, 0.1 equiv) was added, followed by a solution of triflate **169** (50 mg, 67 µmol, 1 equiv) in 1,4-dioxane (0.6 mL). Tributylstannylmethanol (64 mg, 0.20 mmol, 3.0 equiv) was then added and the mixture was heated to 62 °C. After 2 h, heating was ceased and the solution was cooled to 25 °C. The mixture was concentrated. The crude product was purified by flash column chromatography on silica gel (5% to 10% to 20% ethyl acetate in hexanes) to afford allylic alcohol **218** (19.2 mg, 47%) as a colorless oil, which contained minor tin impurities.

4-Methylmorpholine (3.9 mg, 33 µmol, 1.1 equiv) was added to a Schlenk flask containing activated molecular sieves (4 Å, 30 mg) and dichloromethane (0.5 mL) was added. After 10 min,

tetrapropylammonium perruthenate (2.1 mg, 6.1 µmol, 0.20 equiv) was added, followed by a solution of allylic alcohol **218** (19.2 mg, 30.3 µmol, 1 equiv) in dichloromethane (0.3 mL). After 2 h, tetrapropylammonium perruthenate (2.1 mg, 6.1 µmol, 0.20 equiv) was added. After a total of 3 h, the black suspension was filtered through a short plug of celite, covered with silica gel. The filter cake was rinsed with dichloromethane (10 mL). The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethylacetate in hexanes) to afford **219** (10.3 mg, 54%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.36 (UV, CAM).

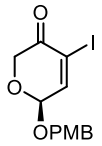
^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.26 (s, 1H), 7.27–7.21 (m, 3H), 6.90–6.83 (m, 2H), 5.36–5.33 (m, 1H), 5.20 (dd, *J* = 2.7, 1.0 Hz, 1H), 4.85–4.83 (m, 1H), 4.81–4.75 (m, 2H), 4.54 (d, *J* = 11.3 Hz, 1H), 3.97 (d, *J* = 1.3 Hz, 2H), 3.83–3.76 (m, 4H), 3.70 (dd, *J* = 9.1, 4.2 Hz, 1H), 2.99 (t, *J* = 2.8 Hz, 1H), 2.67–2.58 (m, 1H), 2.23–2.00 (m, 4H), 1.57 (s, 3H), 0.93–0.87 (m, 18H), 0.53 (q, *J* = 7.8 Hz, 6H), 0.04 (s, 6H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 190.9, 162.9, 160.0, 148.4, 135.5, 130.1, 129.6, 124.1, 119.7, 114.2, 111.0, 102.0, 71.1, 68.9, 61.6, 55.7, 40.2, 36.3, 36.1, 26.3, 26.2, 18.8, 13.8, 7.1, 4.9, −5.1.

HR-MS (ESI): calcd for $(C_{35}H_{59}O_6Si_2)^+$ $(M+H)^+$: 631.3850, found: 631.3842.

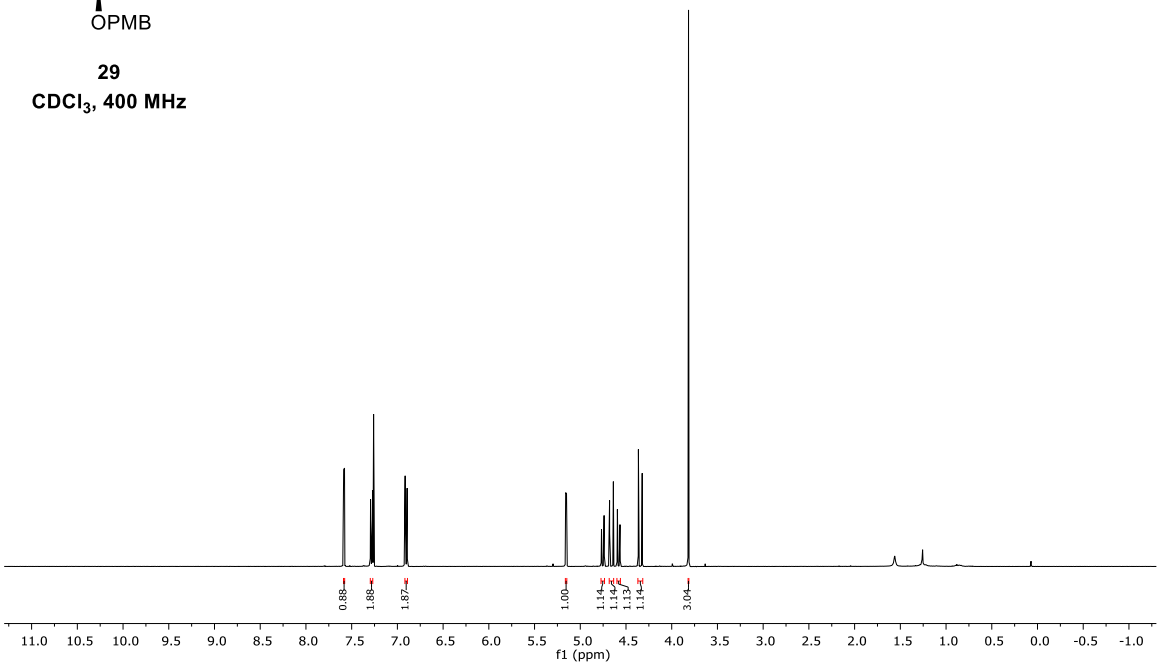
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2933, 2878, 2857, 1677, 1636, 1515, 1463, 1251, 1176, 1091 cm^{-1}.

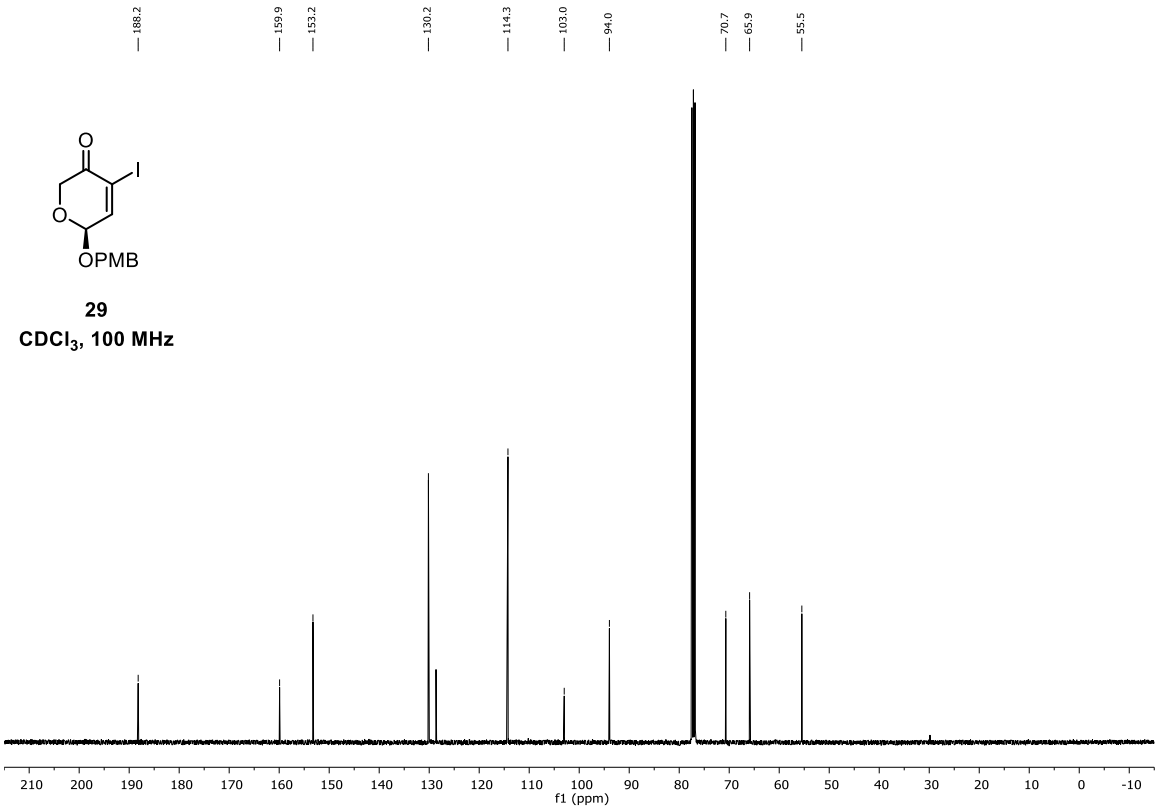
$[\boldsymbol{\alpha}]_{589}^{20}$ = +121.4 (c = 1.0 · 10 g · mL^{-1}, CH_2Cl_2).

9.3 ^{1}H and ^{13}C NMR Spectra

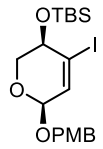


29
$CDCl_3$, 400 MHz

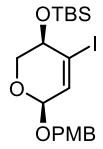




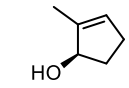
29
$CDCl_3$, 100 MHz



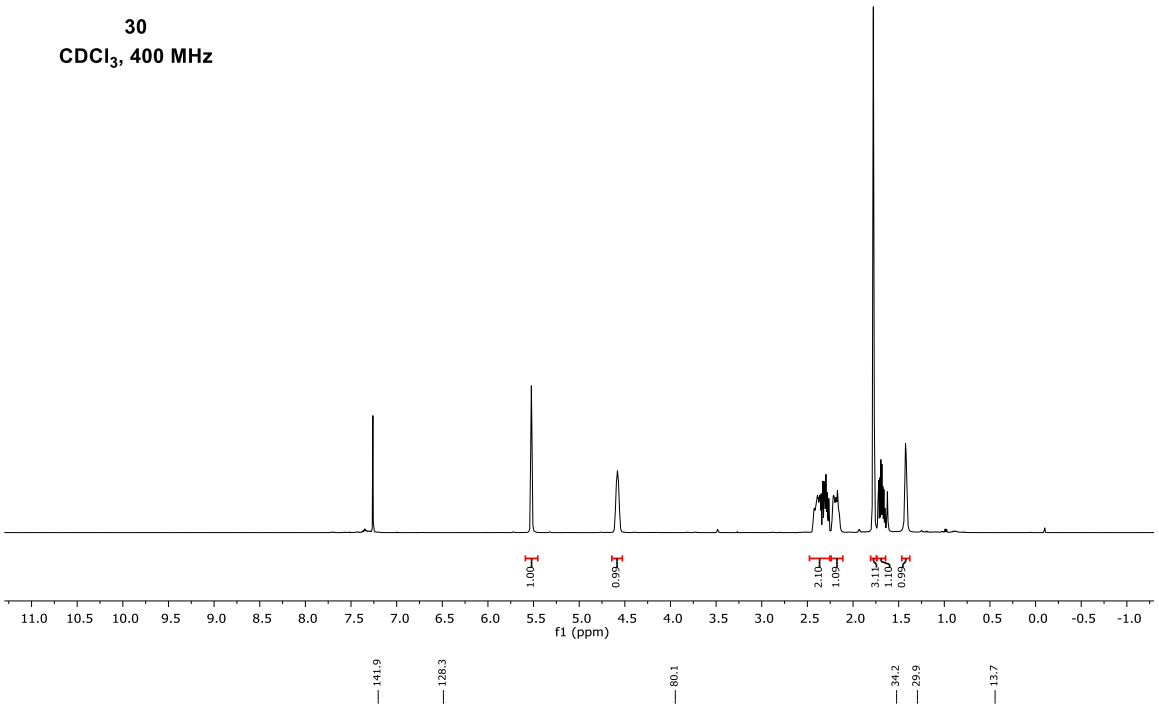
18
$CDCl_3$, 400 MHz

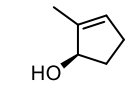


18
$CDCl_3$, 100 MHz

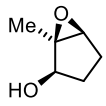


30
$CDCl_3$, 400 MHz

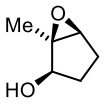




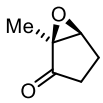
30
$CDCl_3$, 100 MHz



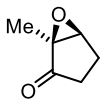
31
CD_2Cl_2, 400 MHz



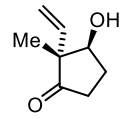
31
CD_2Cl_2, 100 MHz



32
$CDCl_3$, 400 MHz

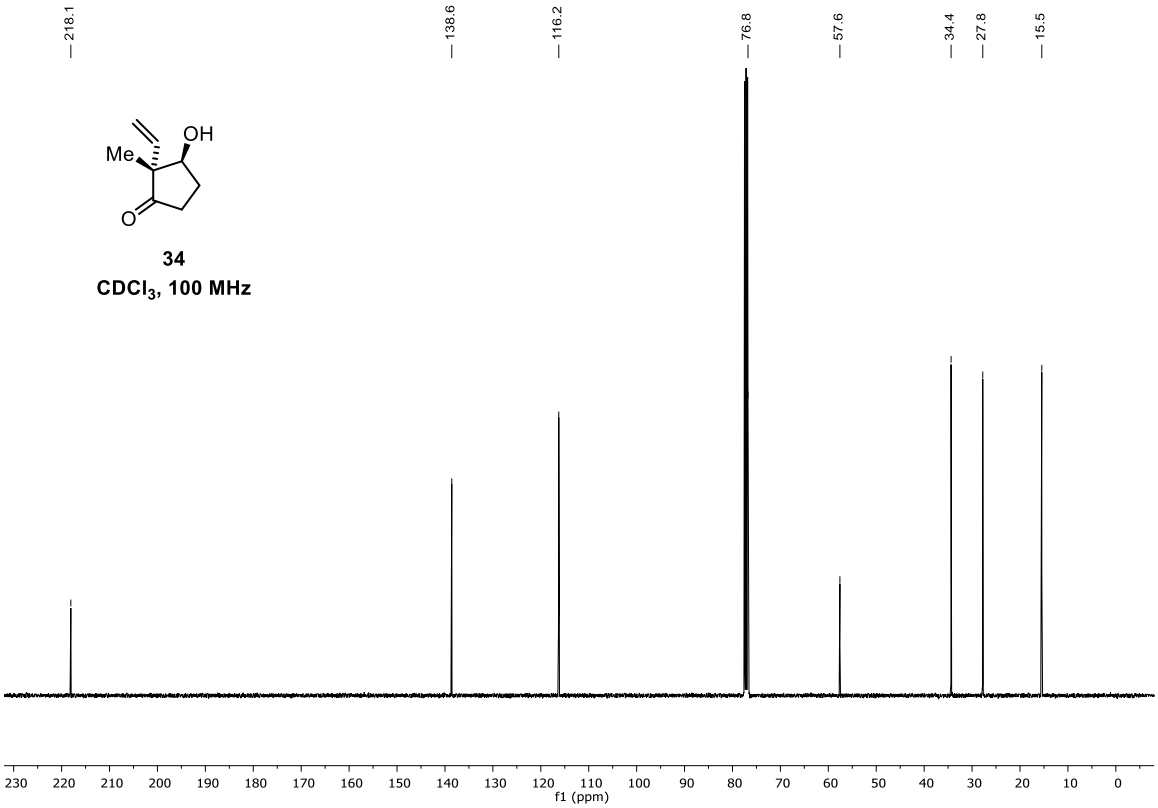


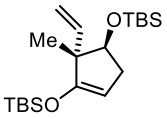
32
$CDCl_3$, 100 MHz



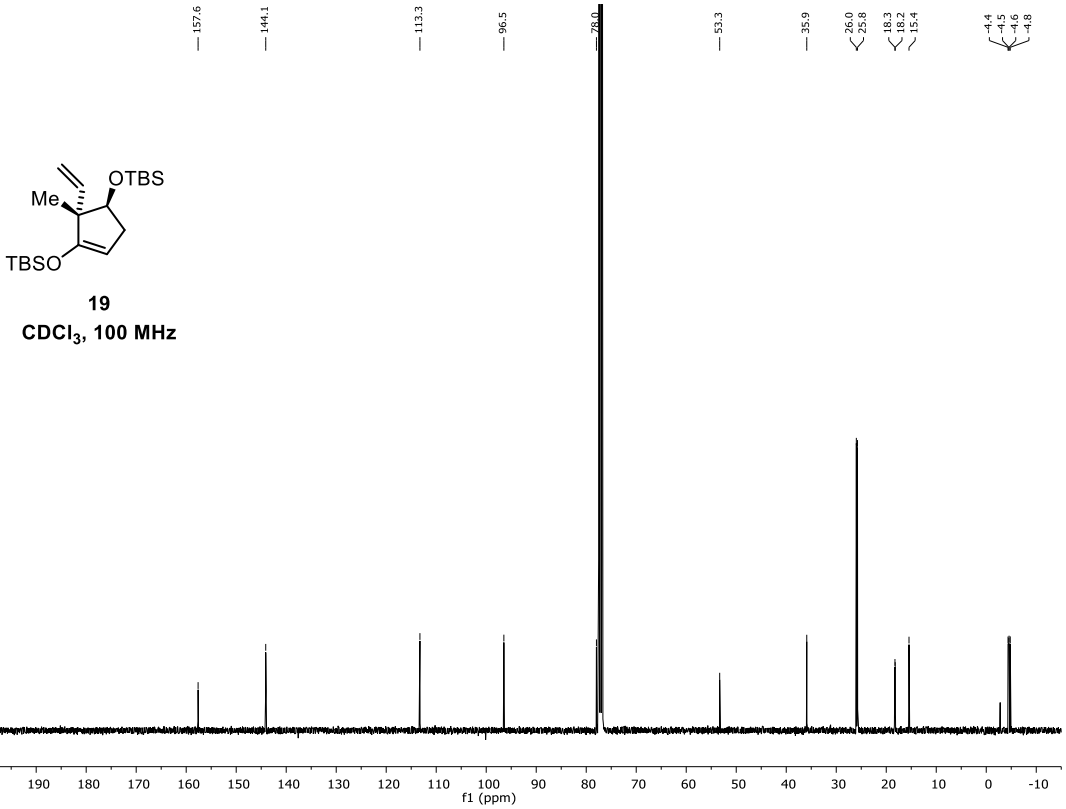
34
$CDCl_3$, 400 MHz

34
$CDCl_3$, 100 MHz

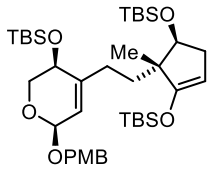




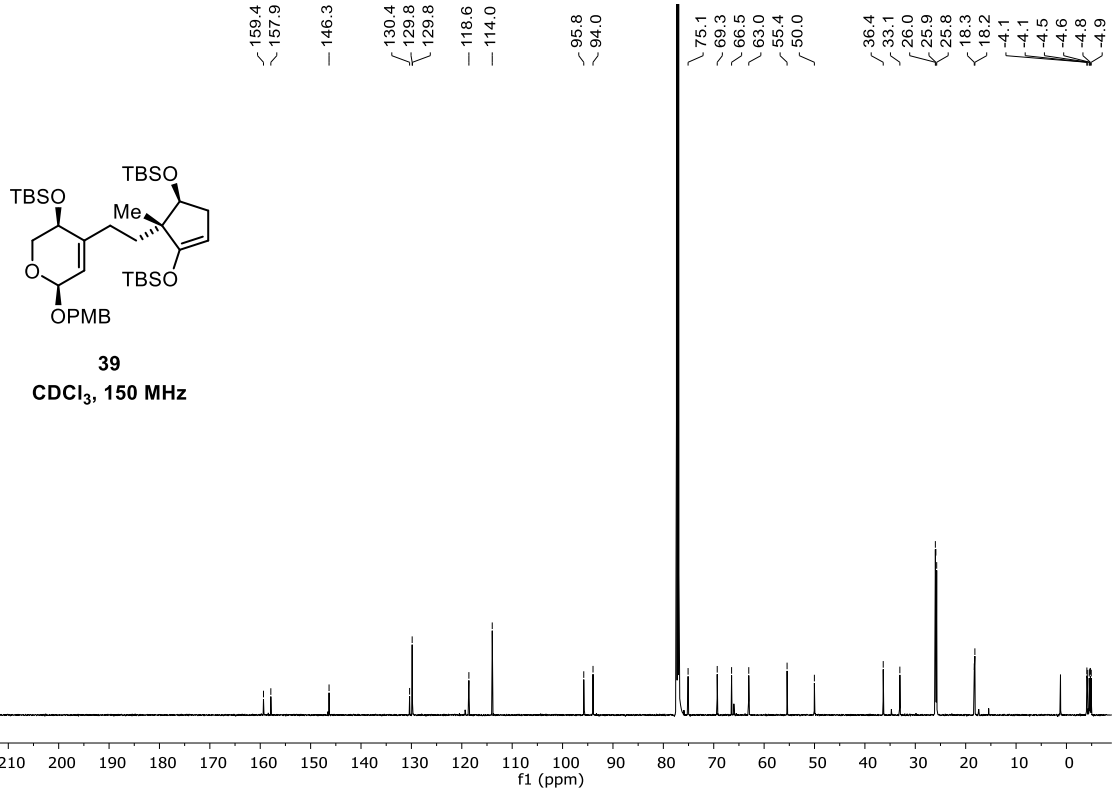
19
$CDCl_3$, 400 MHz



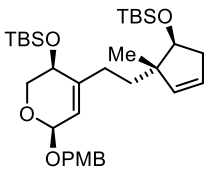
19
$CDCl_3$, 100 MHz



39
$CDCl_3$, 600 MHz

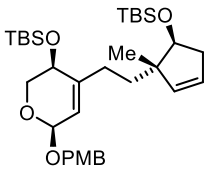


39
$CDCl_3$, 150 MHz



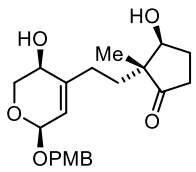
38

$CDCl_3$, 599 MHz

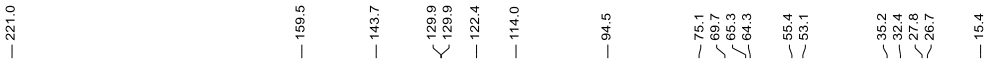


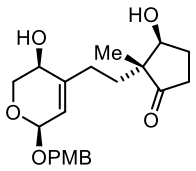
38

$CDCl_3$, 151 MHz

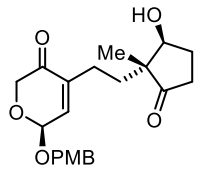


44
$CDCl_3$, 600 MHz

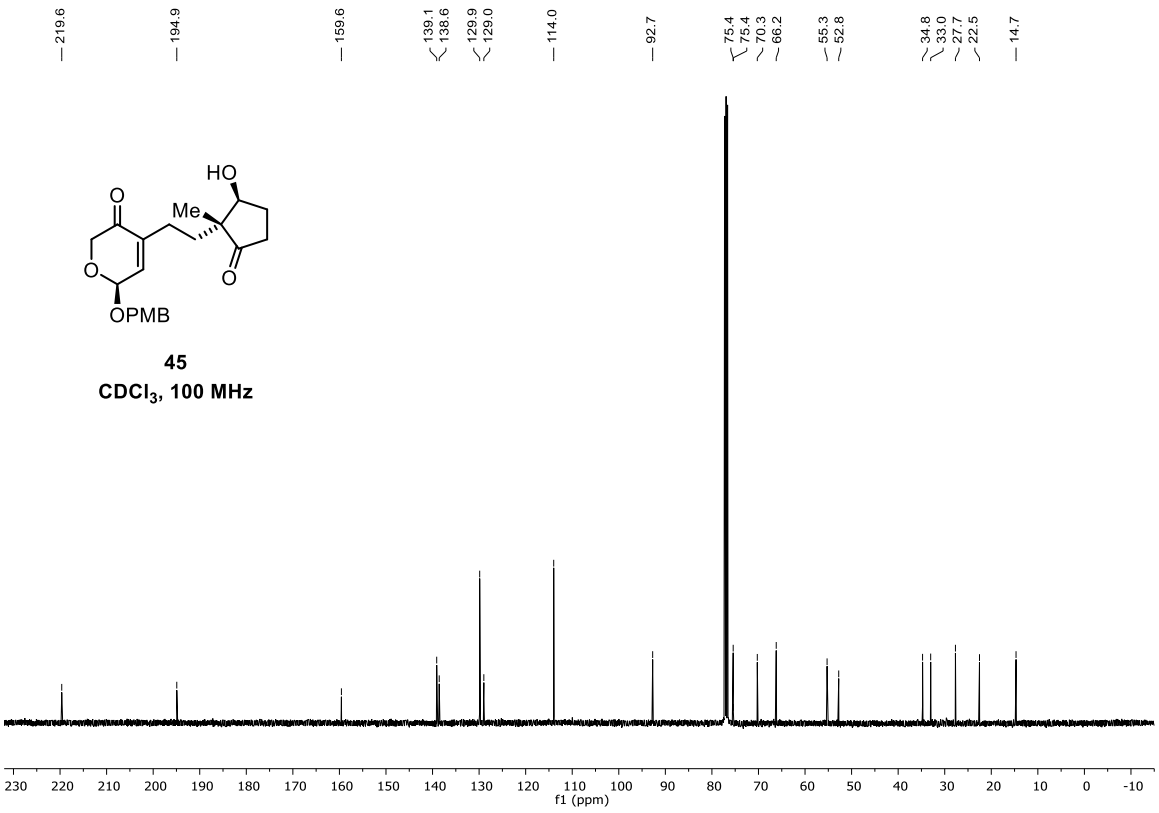




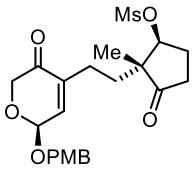
44
$CDCl_3$, 150 MHz



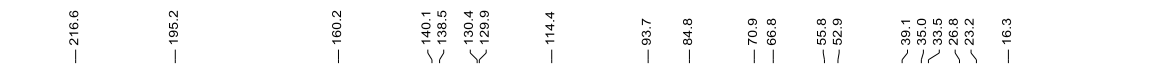
45
$CDCl_3$, 400 MHz

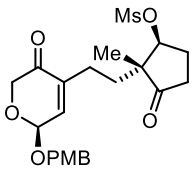


45
$CDCl_3$, 100 MHz

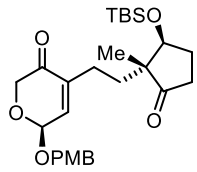


48
CD_2Cl_2, 400 MHz

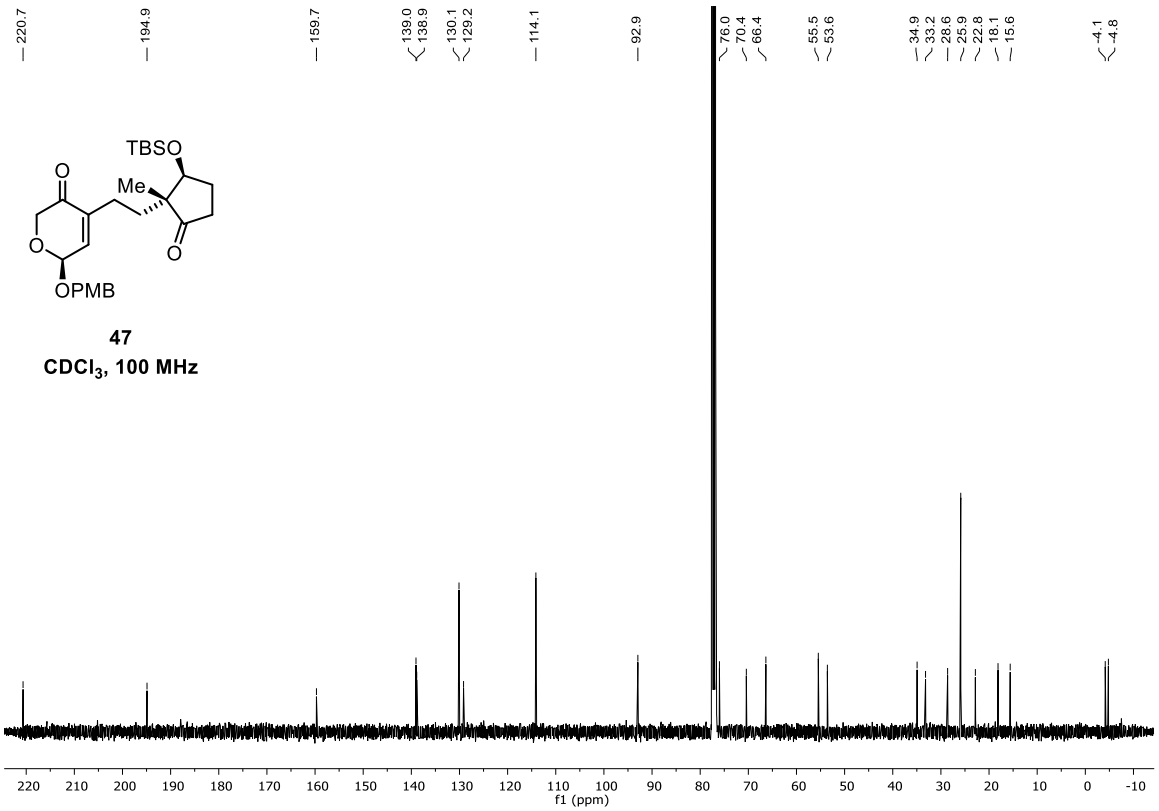




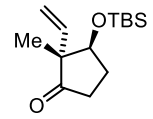
48
CD_2Cl_2, 100 MHz



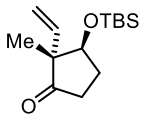
47
$CDCl_3$, 400 MHz



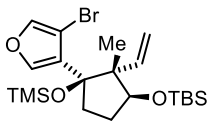
47
$CDCl_3$, 100 MHz



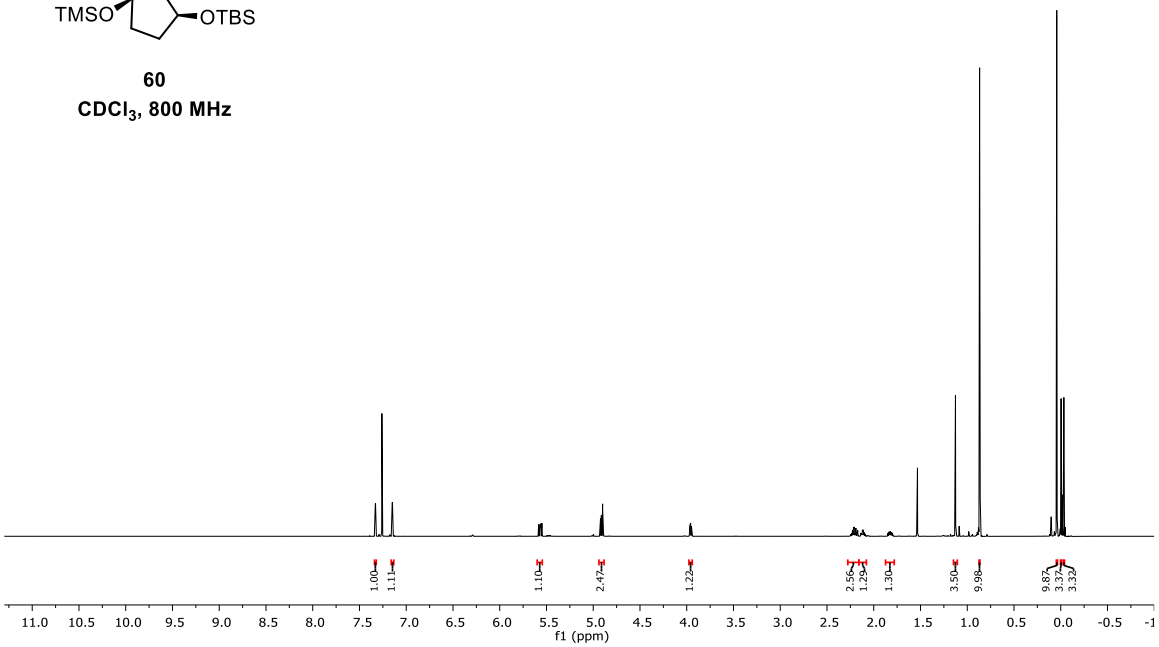
58
$CDCl_3$, 400 MHz

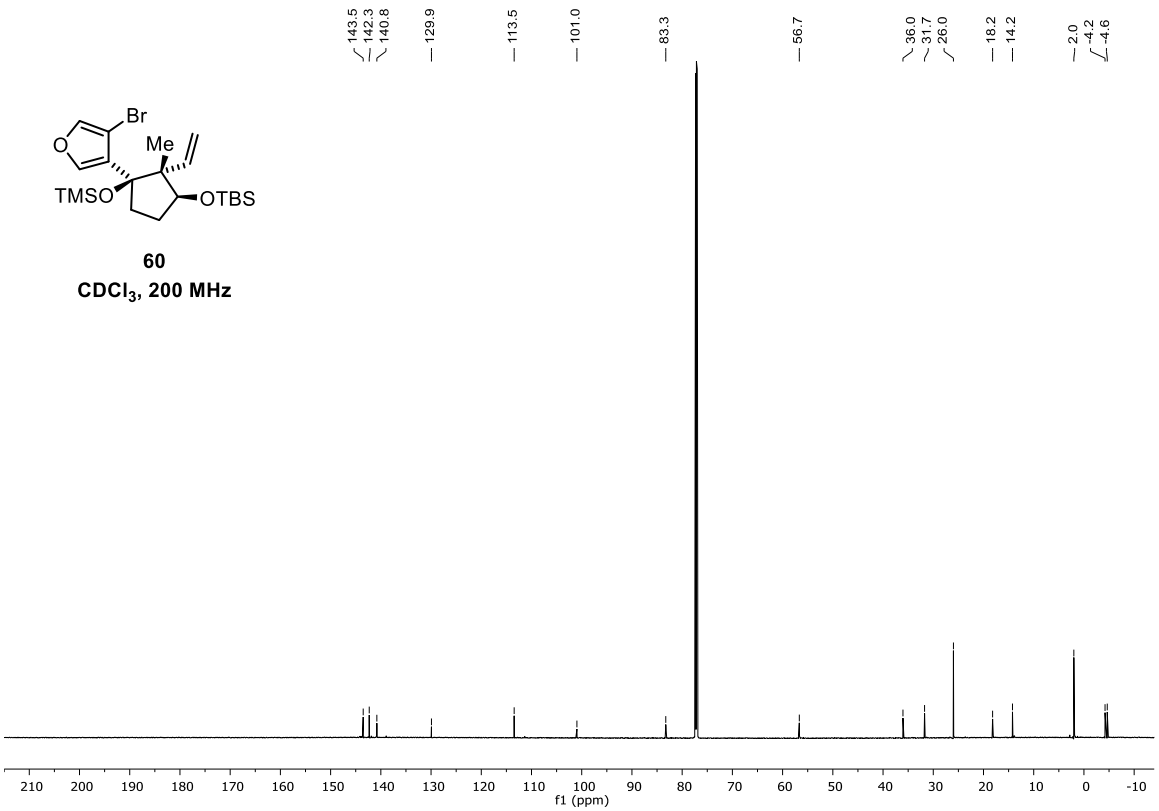


58
$CDCl_3$, 101 MHz

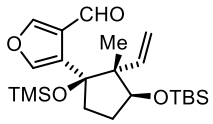


60
$CDCl_3$, 800 MHz

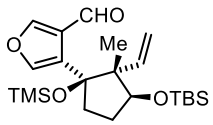




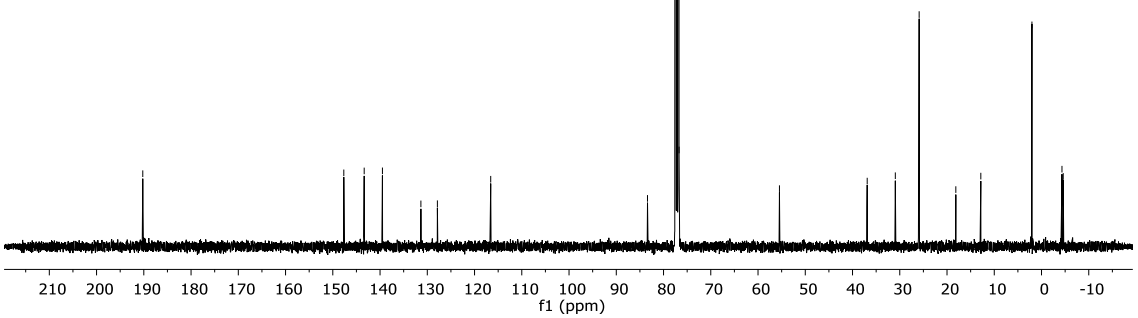
60
$CDCl_3$, 200 MHz

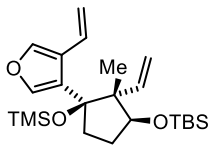


61
$CDCl_3$, 400 MHz

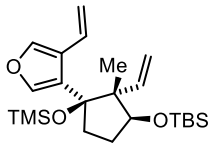


61
$CDCl_3$, 100 MHz

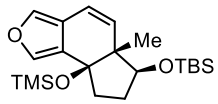




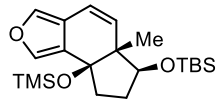
63
C_6D_6, 400 MHz



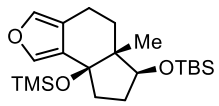
63
C_6D_6, 100 MHz



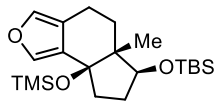
64
CD_2Cl_2, 400 MHz



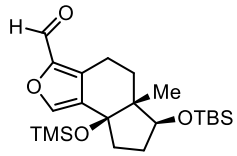
64
CD_2Cl_2, 100 MHz



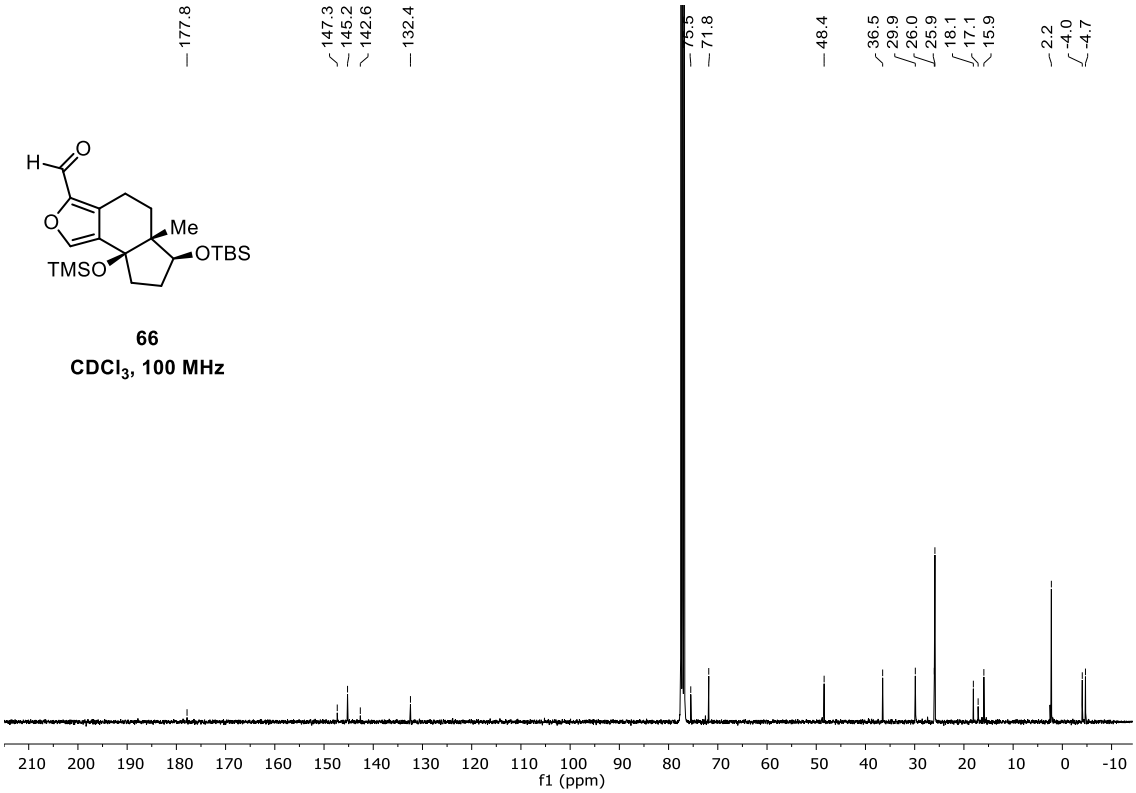
65
CD_2Cl_2, 400 MHz



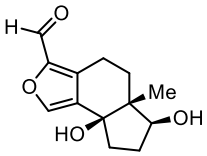
65
CD_2Cl_2, 100 MHz



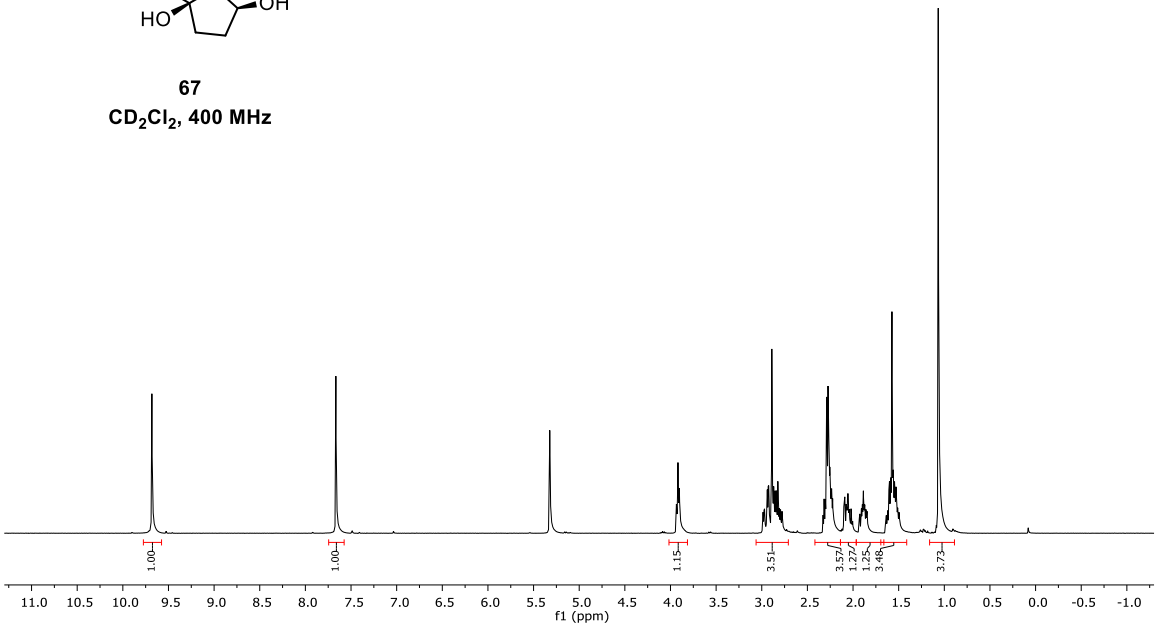
66
$CDCl_3$, 400 MHz

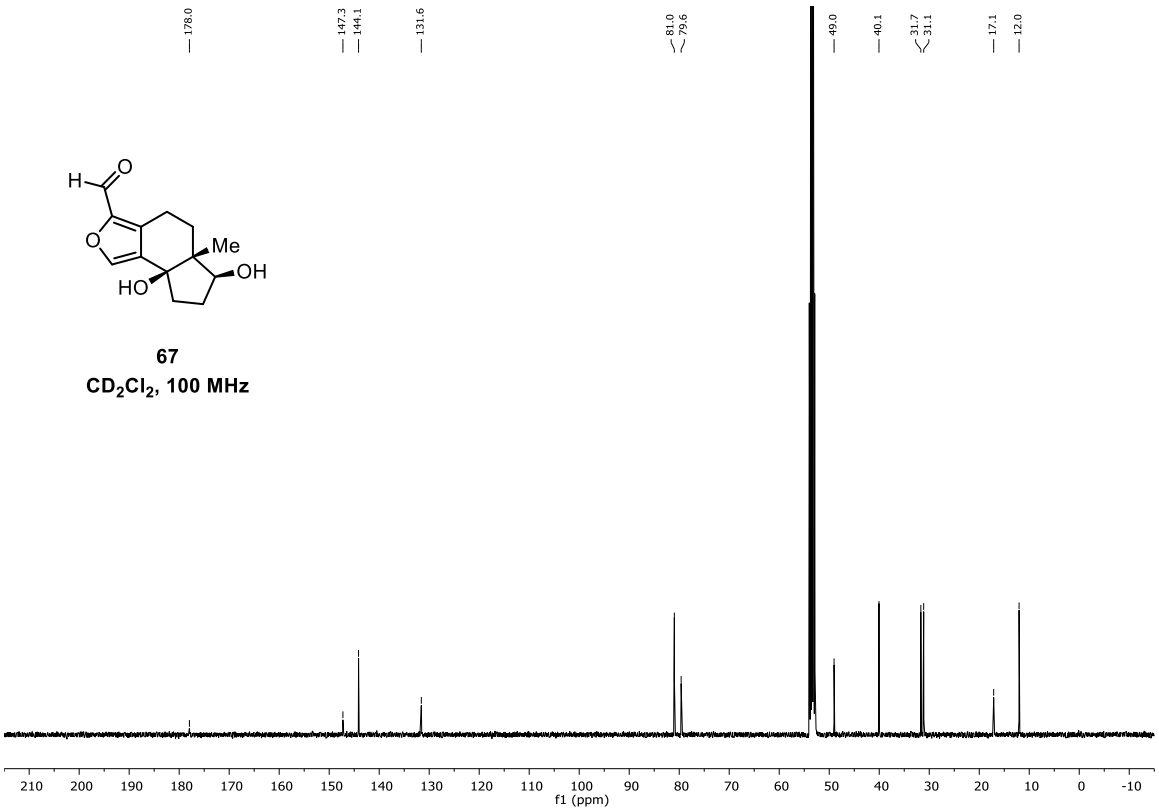


66
$CDCl_3$, 100 MHz

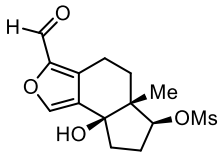


67
CD_2Cl_2, 400 MHz

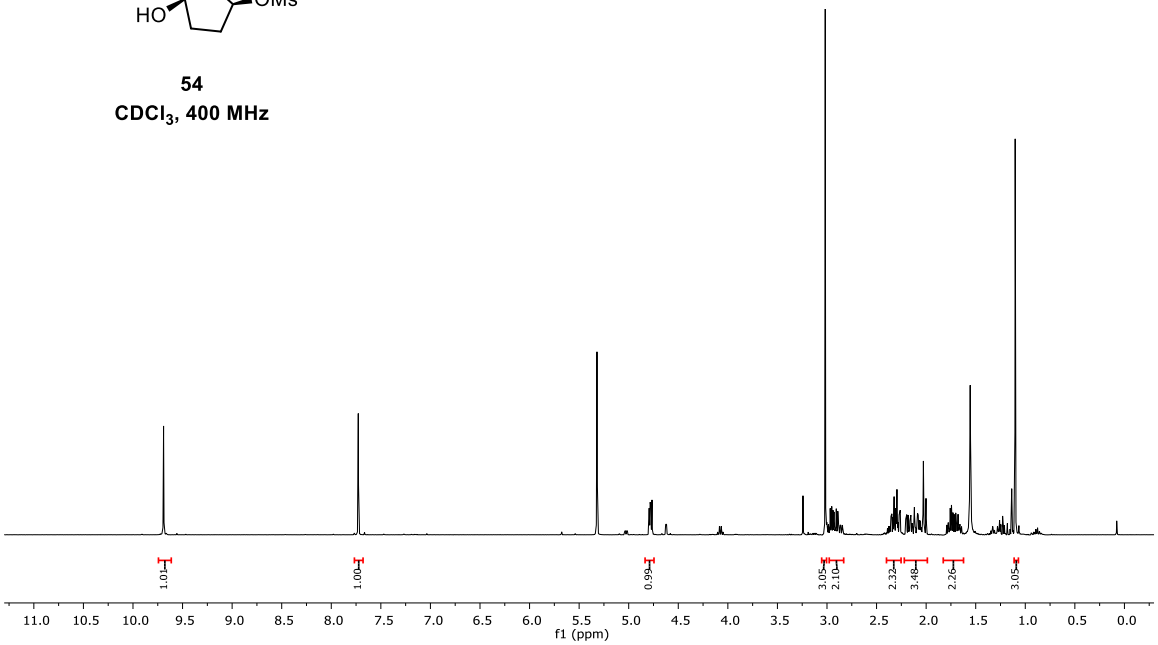


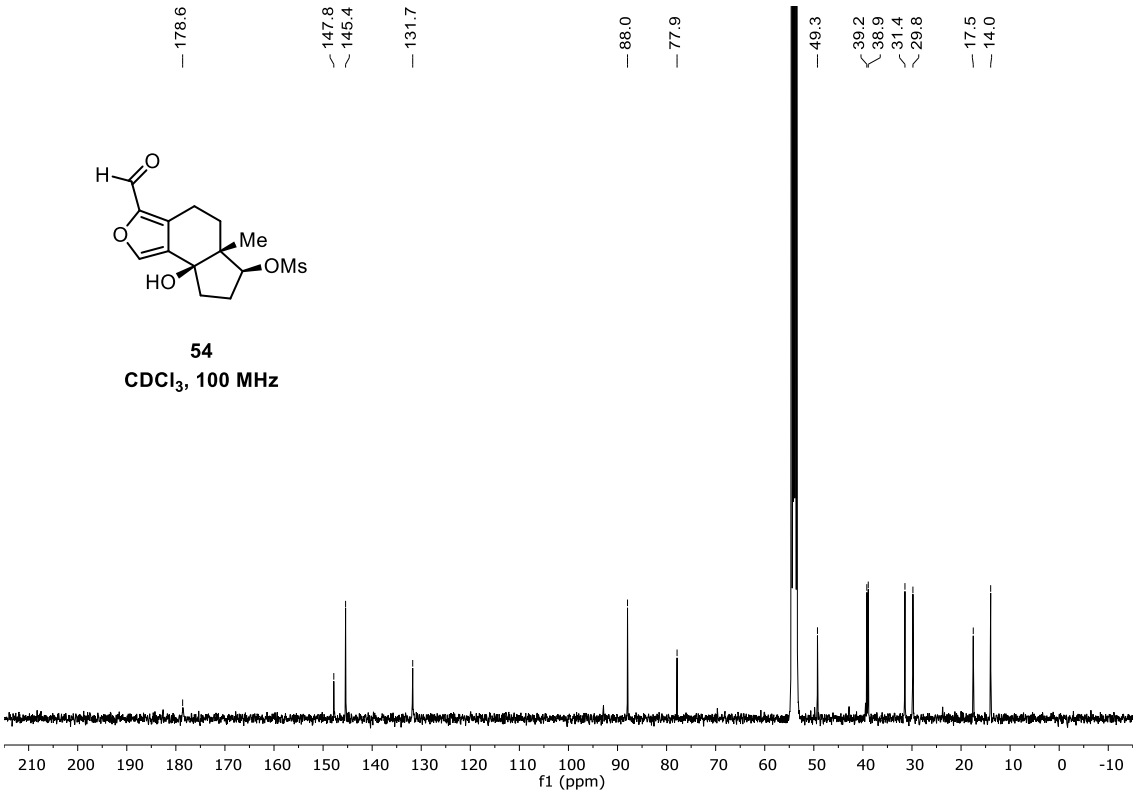


67
CD_2Cl_2, 100 MHz

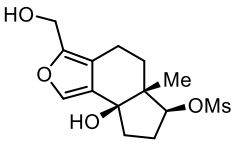


54
$CDCl_3$, 400 MHz

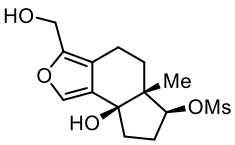




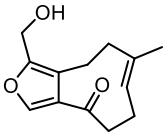
54
$CDCl_3$, 100 MHz



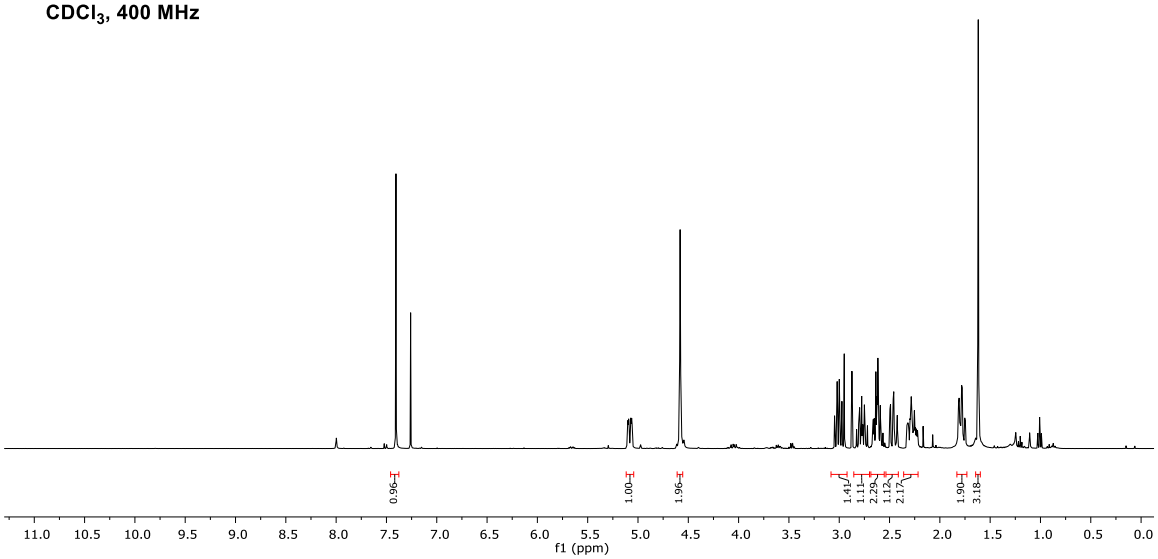
69
CD_2Cl_2, 800 MHz

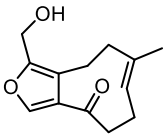


69
CD_2Cl_2, 200 MHz

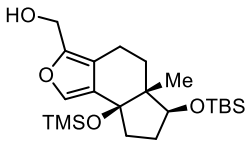


53
$CDCl_3$, 400 MHz

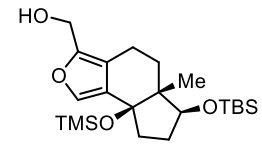




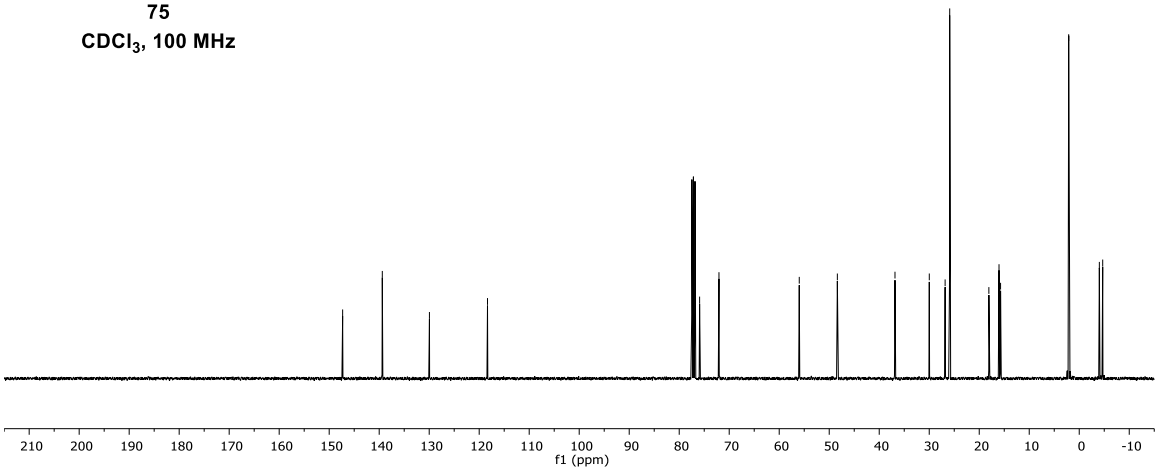
53
$CDCl_3$, 100 MHz

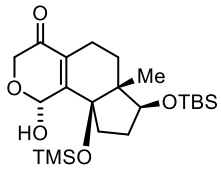


75
$CDCl_3$, 400 MHz



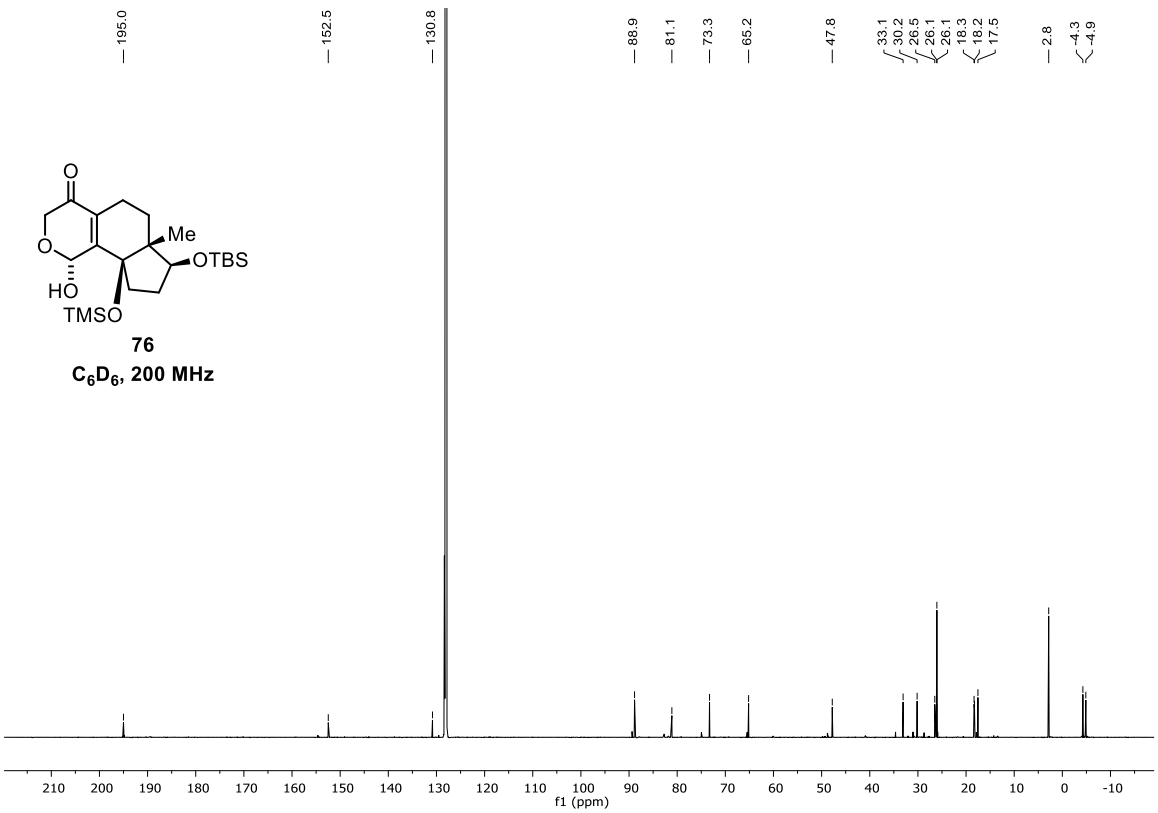
75
$CDCl_3$, 100 MHz





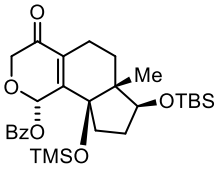
76

C_6D_6, 800 MHz



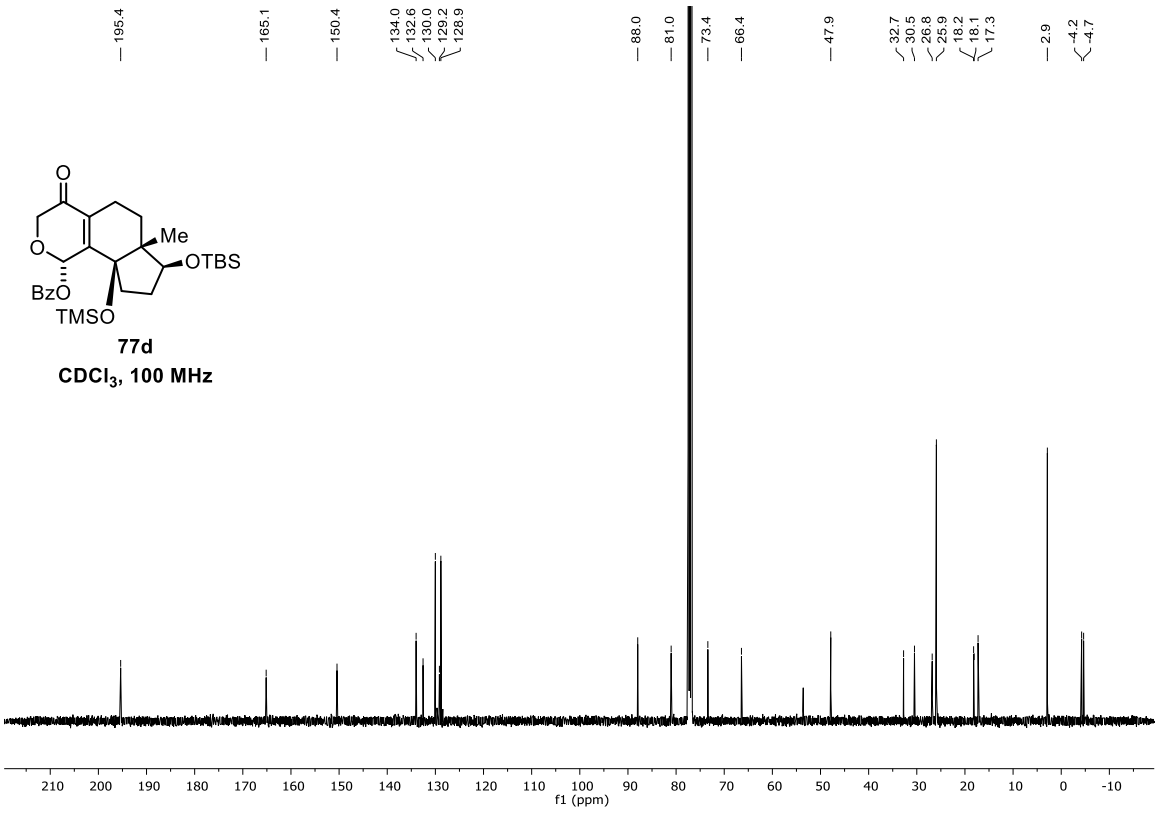
76

C_6D_6, 200 MHz



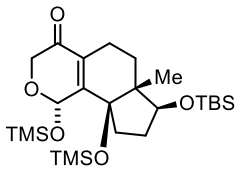
77d

$CDCl_3$, 400 MHz



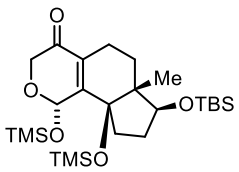
77d

$CDCl_3$, 100 MHz



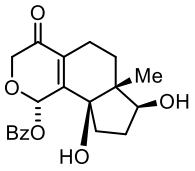
77f

CD_2Cl_2, 400 MHz

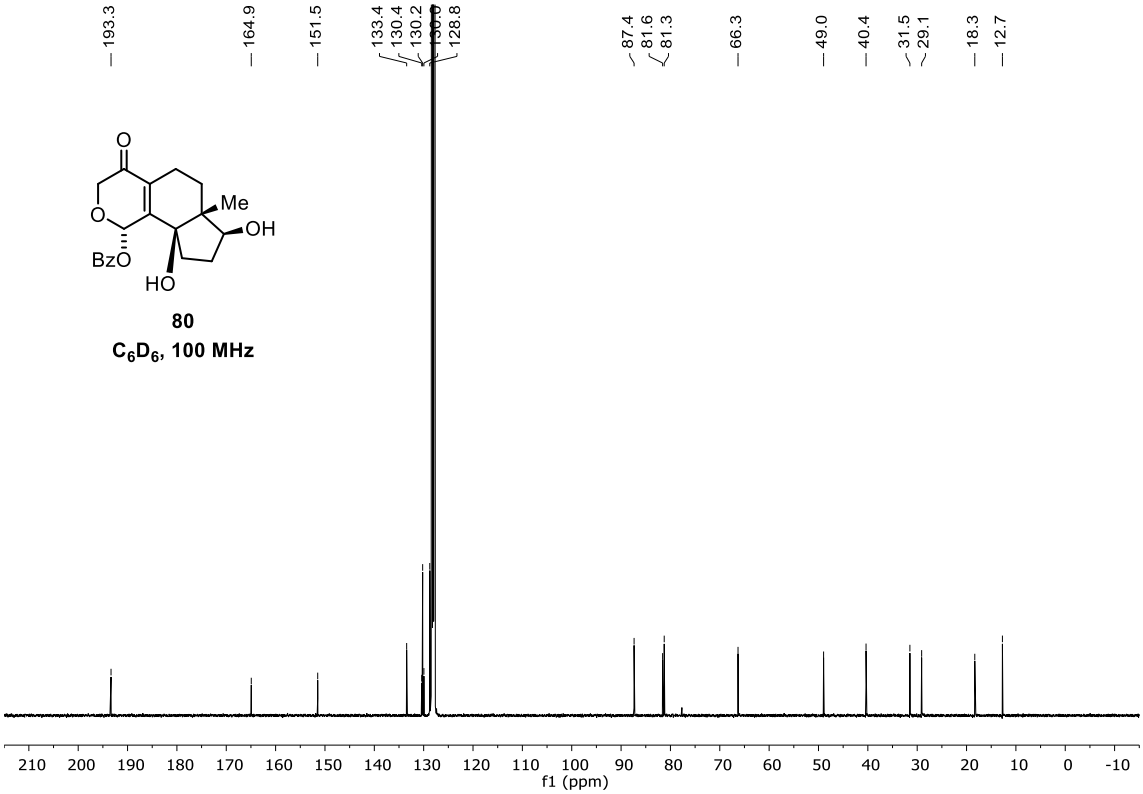


77f

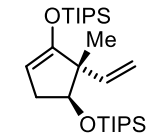
CD_2Cl_2, 100 MHz



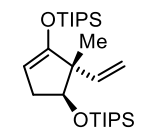
80
C_6D_6, 400 MHz



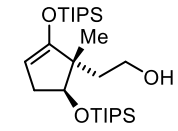
80
C_6D_6, 100 MHz



103
$CDCl_3$, 400 MHz

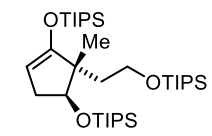


103
$CDCl_3$, 100 MHz



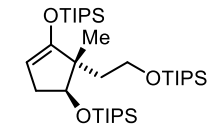
104

$CDCl_3$, 200 MHz



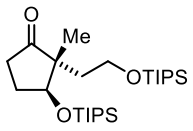
S1

$CDCl_3$, 400 MHz

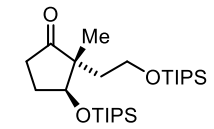


S1

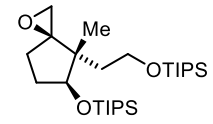
$CDCl_3$, 100 MHz



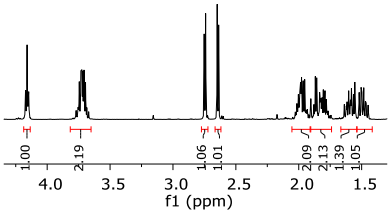
105
$CDCl_3$, 400 MHz

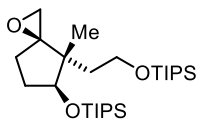


105
$CDCl_3$, 100 MHz

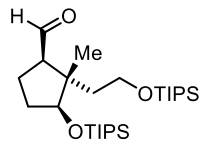


106
$CDCl_3$, 400 MHz

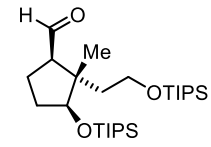




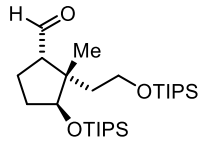
106
$CDCl_3$, 100 MHz



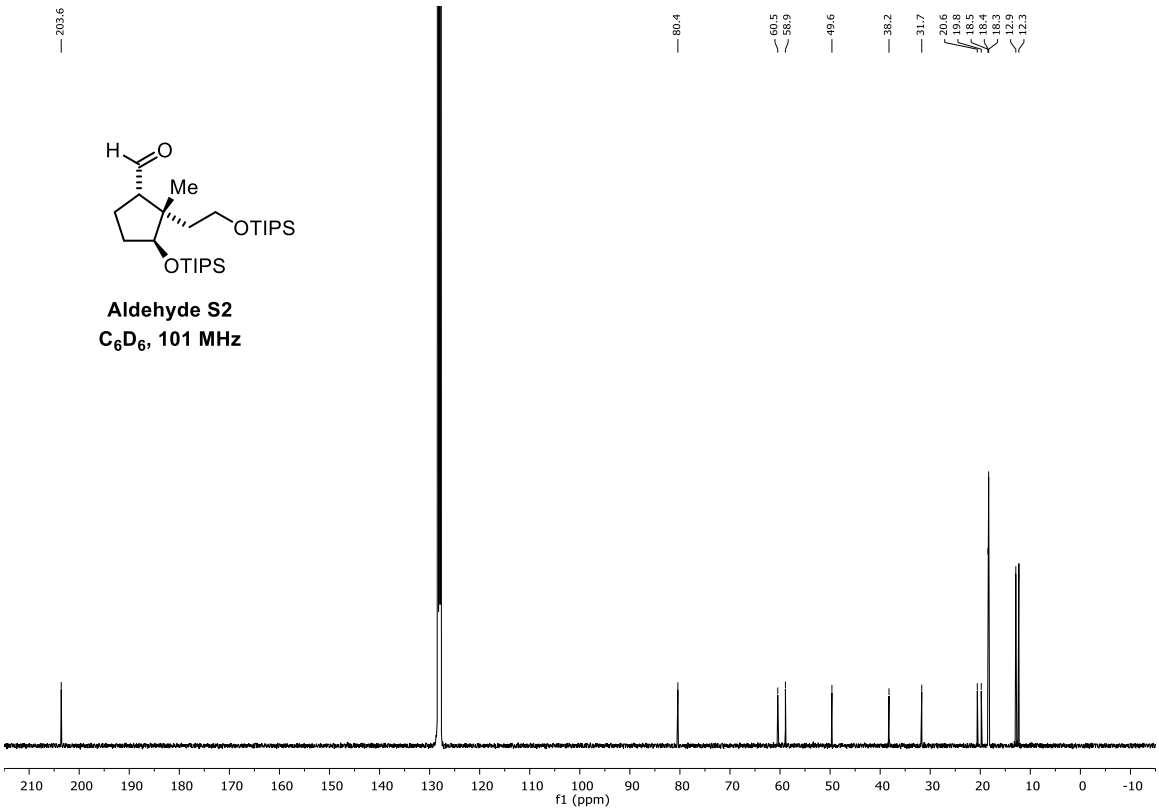
107
C_6D_6, 400 MHz



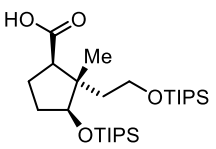
107
C_6D_6, 101 MHz



Aldehyde S2
C_6D_6, 400 MHz

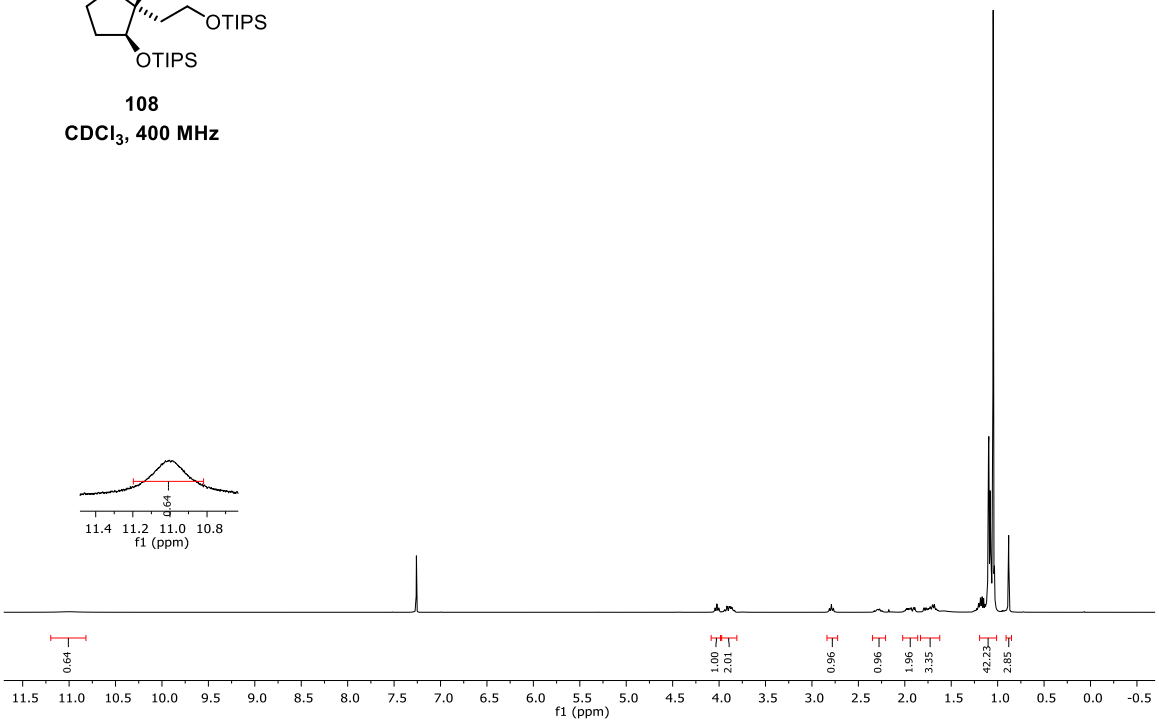


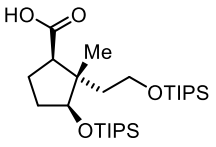
Aldehyde S2
C_6D_6, 101 MHz



108

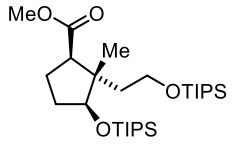
$CDCl_3$, 400 MHz



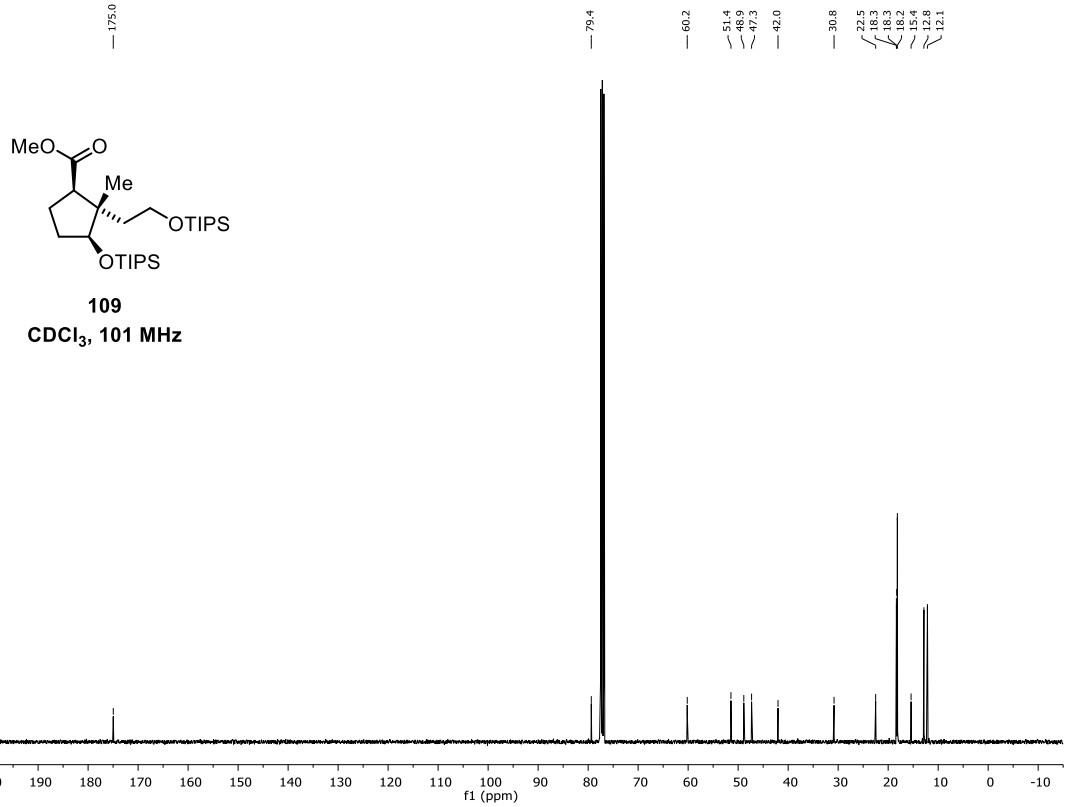


108

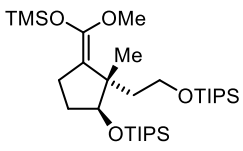
$CDCl_3$, 101 MHz



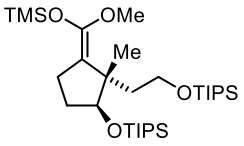
109
$CDCl_3$, 400 MHz



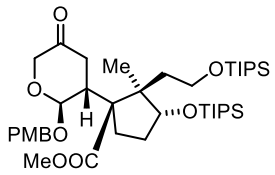
109
$CDCl_3$, 101 MHz



97
C_6D_6, 800 MHz

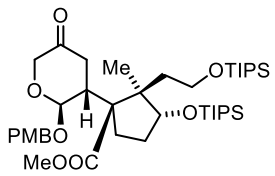


97
C_6D_6, 201 MHz



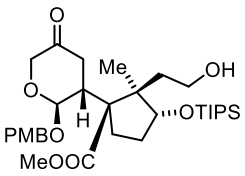
96

$CDCl_3$, 400 MHz

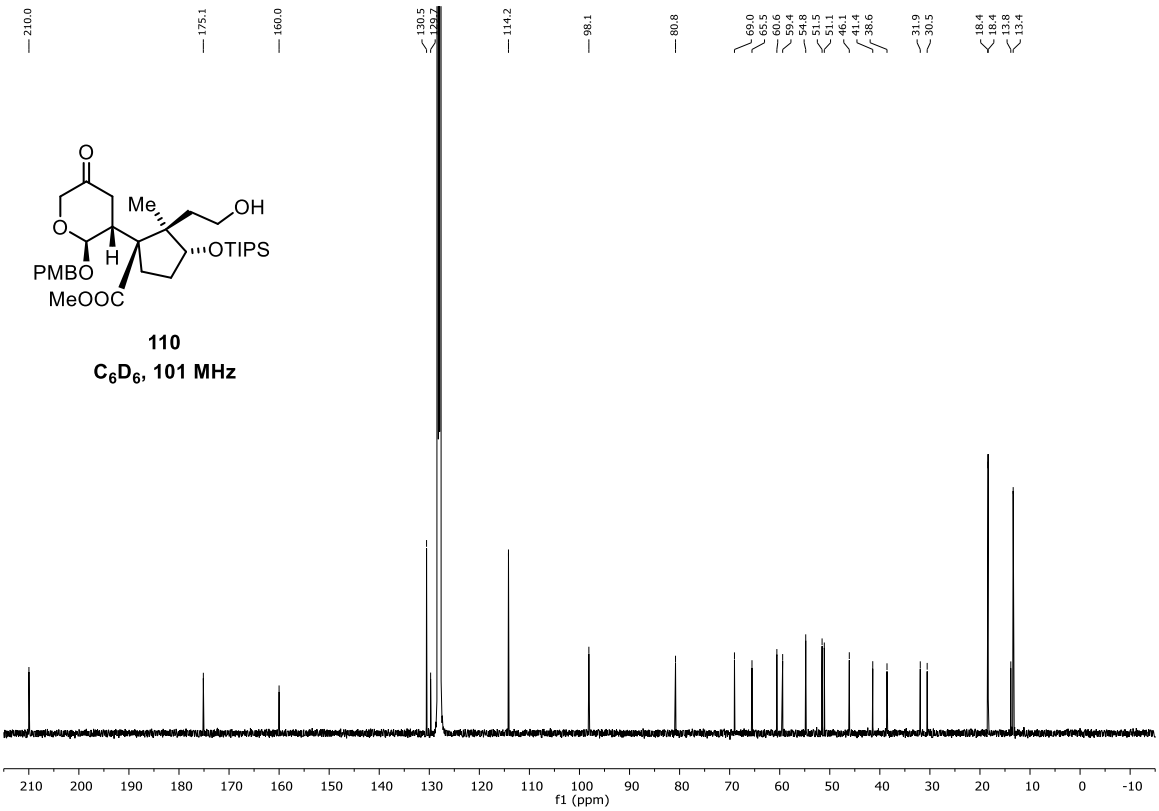


96

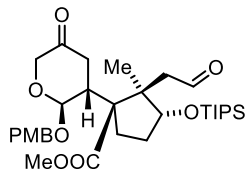
$CDCl_3$, 101 MHz



110
C_6D_6, 400 MHz

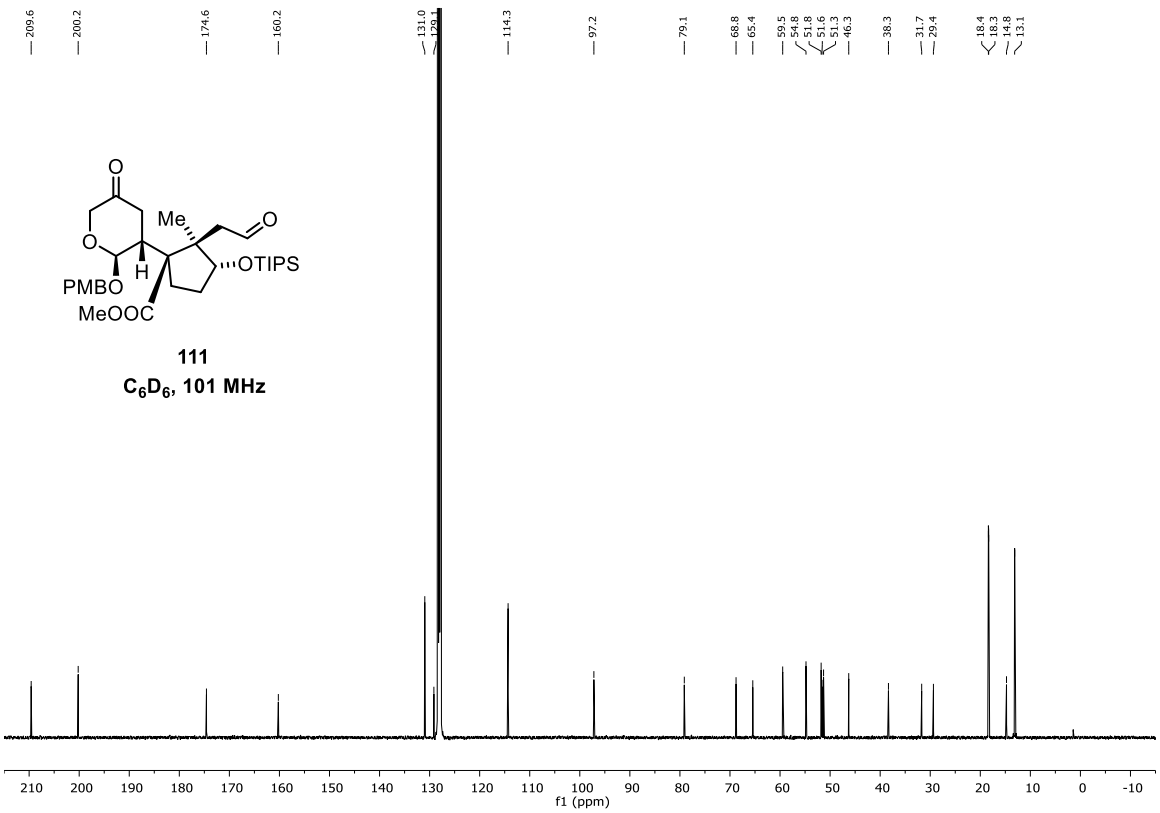


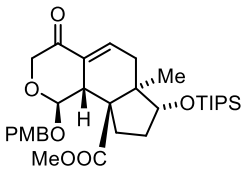
110
C_6D_6, 101 MHz



111
C_6D_6, 400 MHz

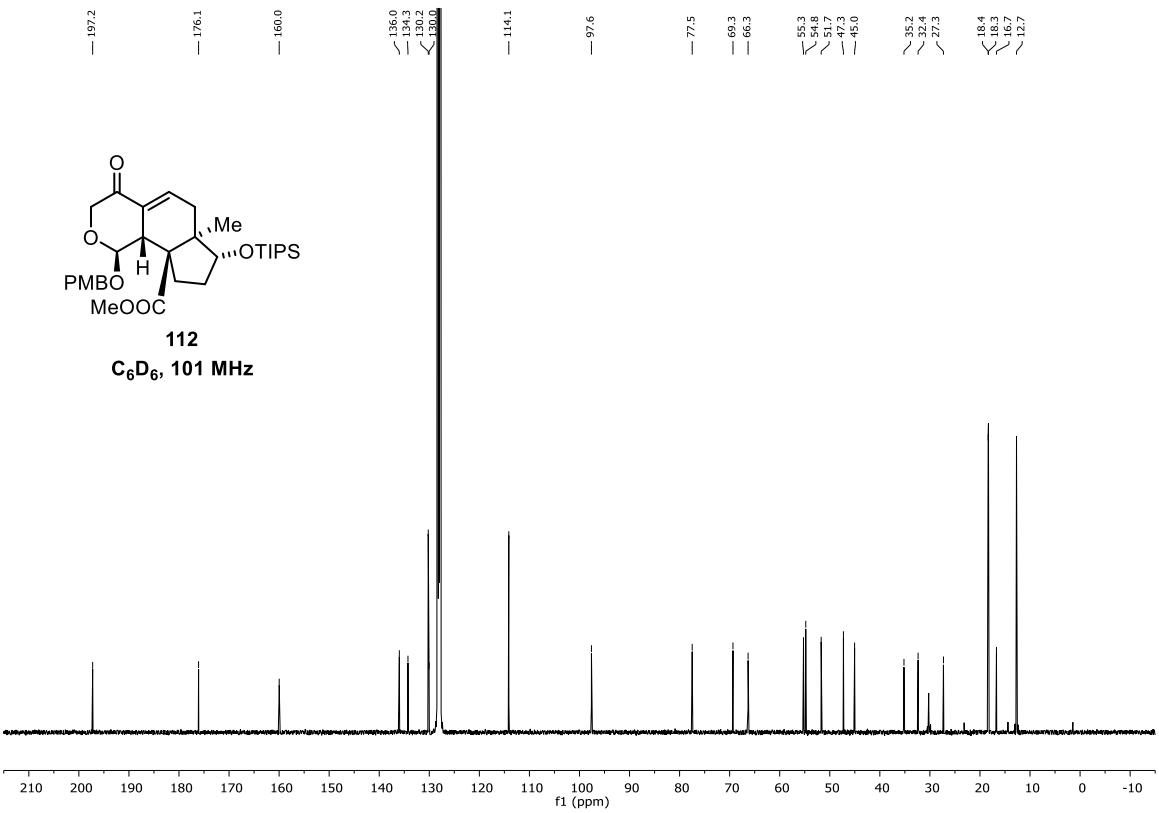
111
C_6D_6, 101 MHz





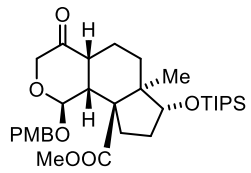
112

C_6D_6, 400 MHz



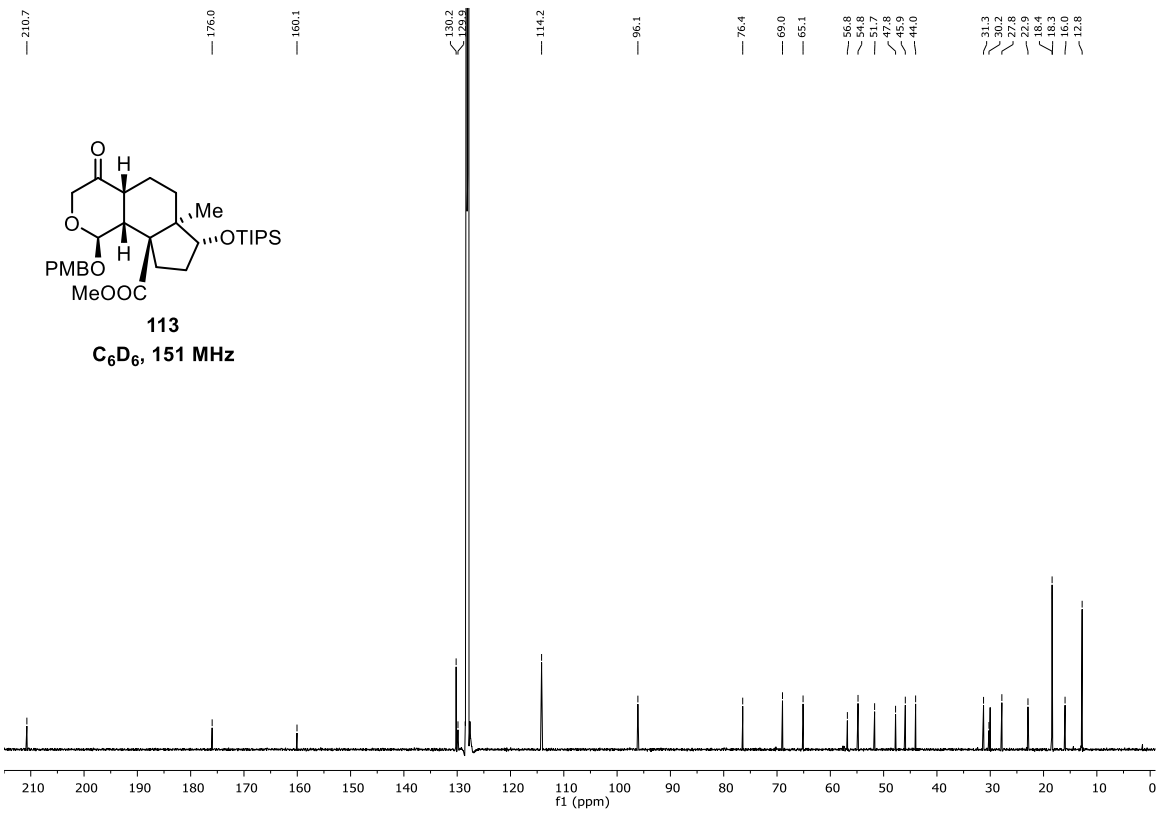
112

C_6D_6, 101 MHz



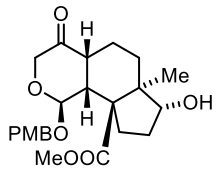
113

C_6D_6, 400 MHz



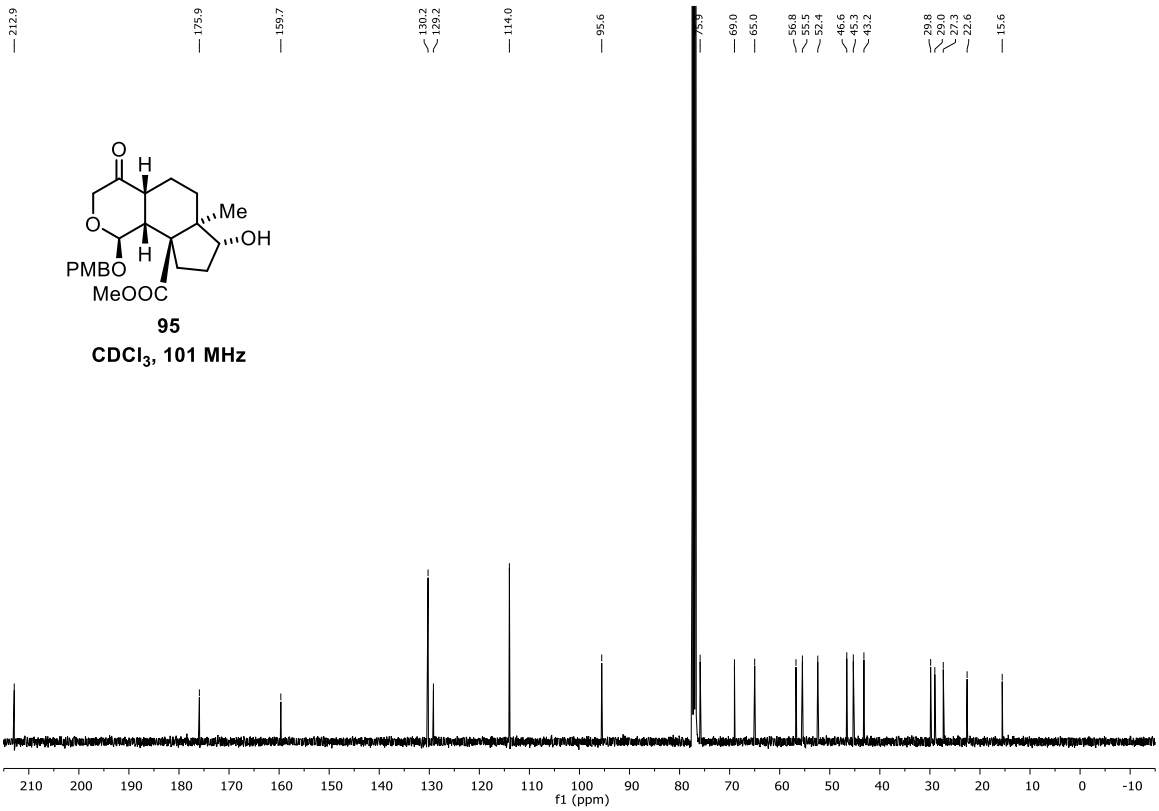
113

C_6D_6, 151 MHz



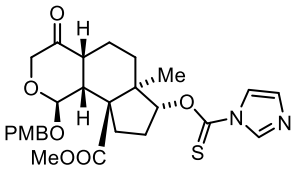
95

$CDCl_3$, 400 MHz



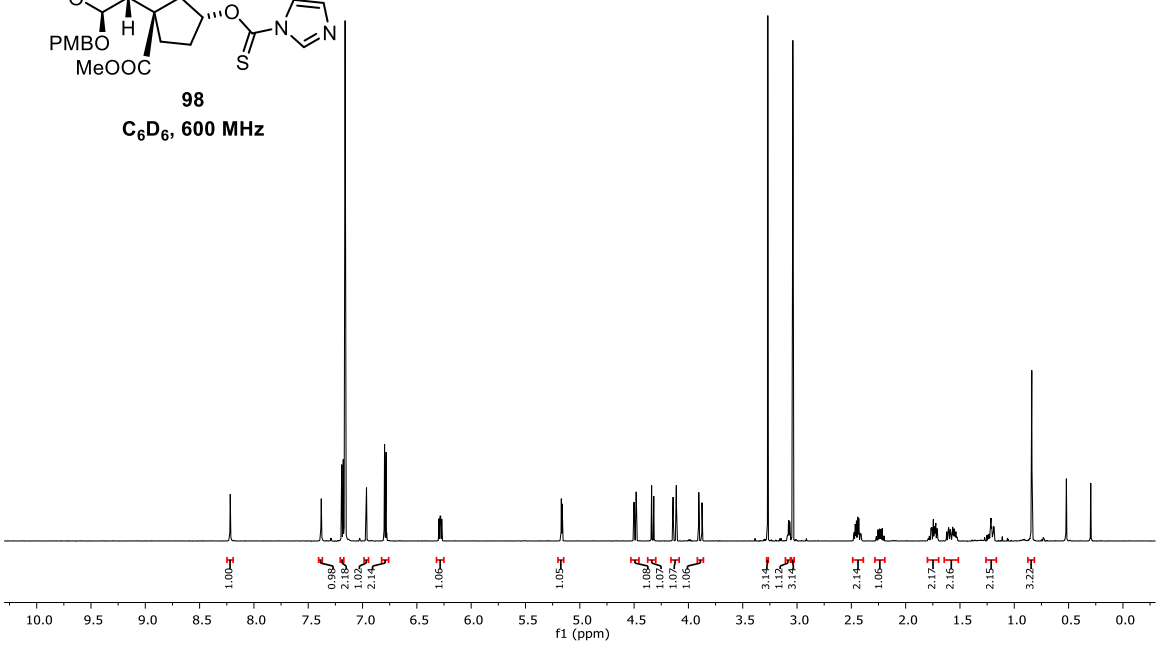
95

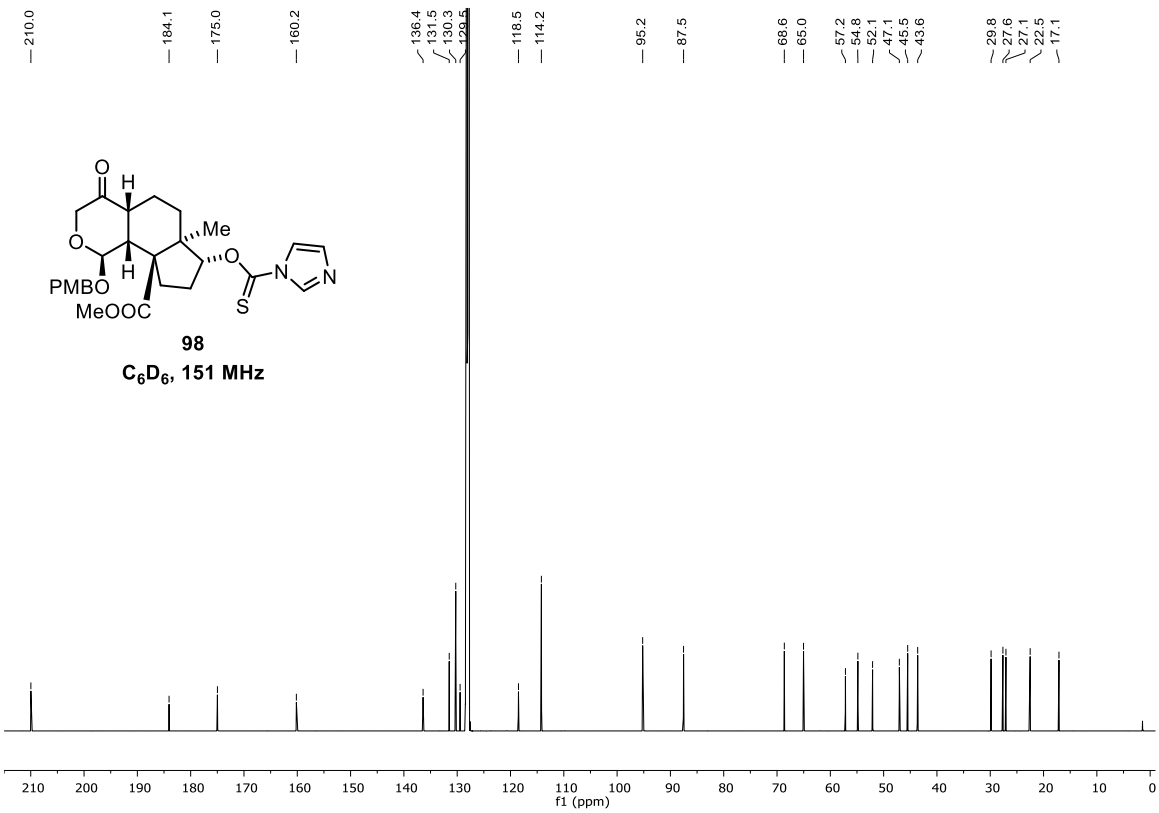
$CDCl_3$, 101 MHz



98

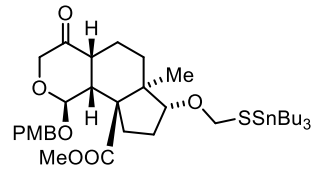
C_6D_6, 600 MHz





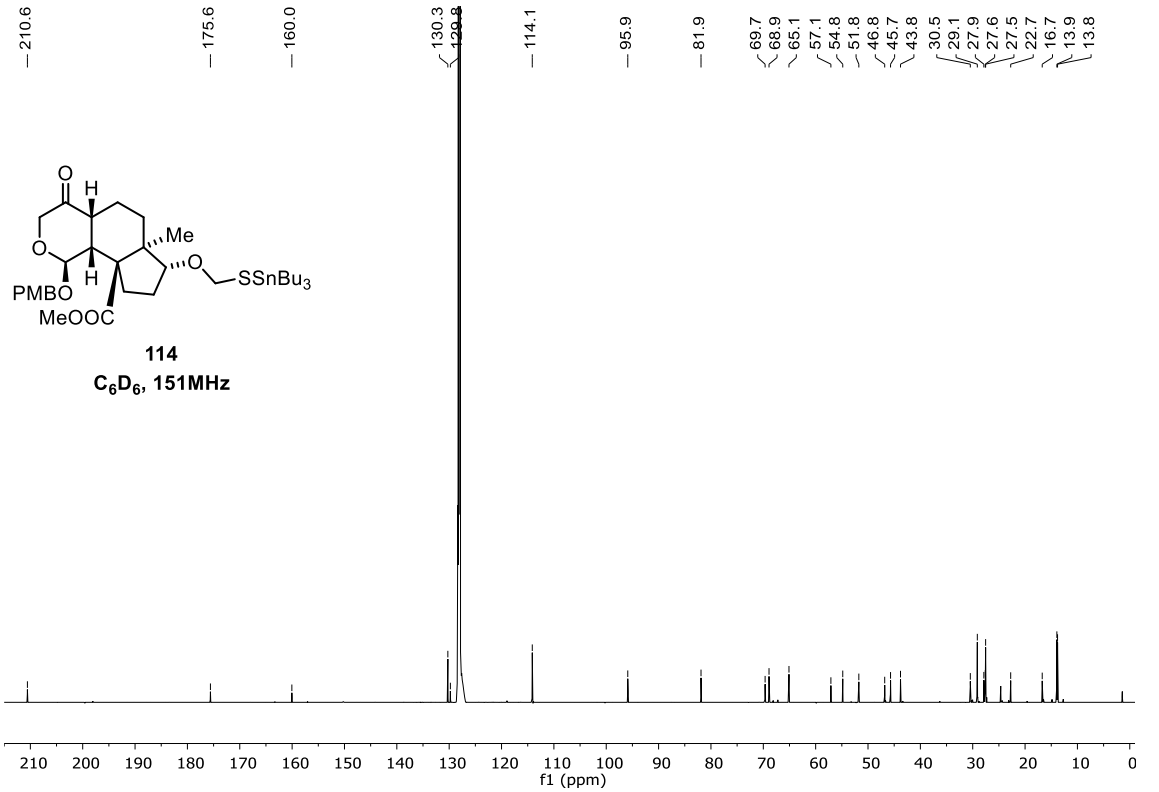
98

C_6D_6, 151 MHz



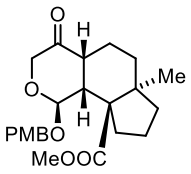
114

C_6D_6, 600 MHz



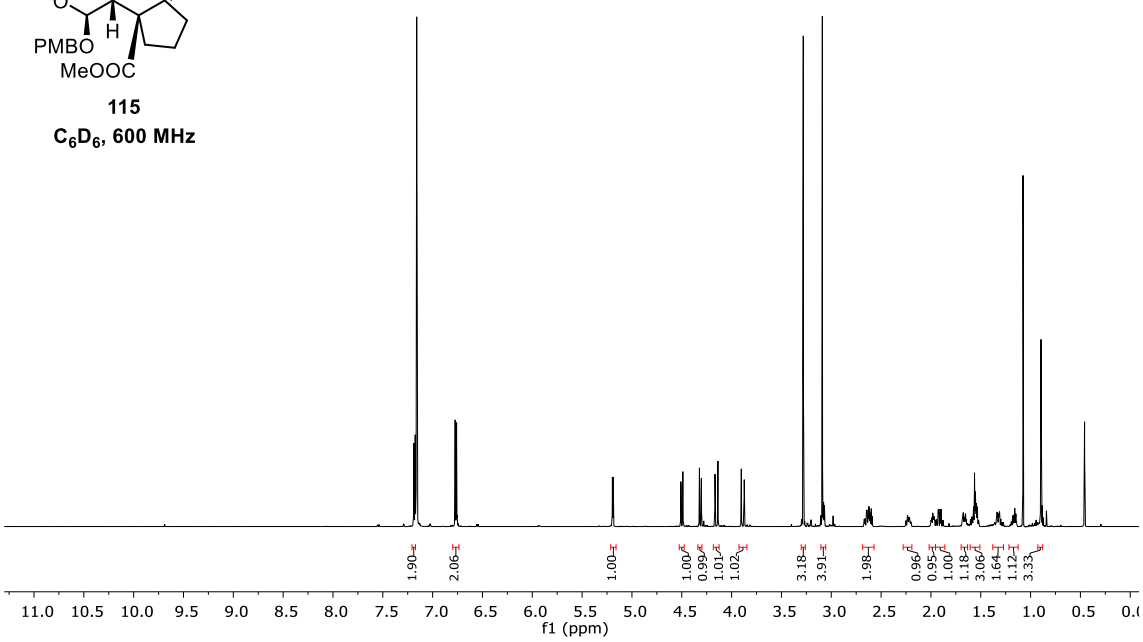
114

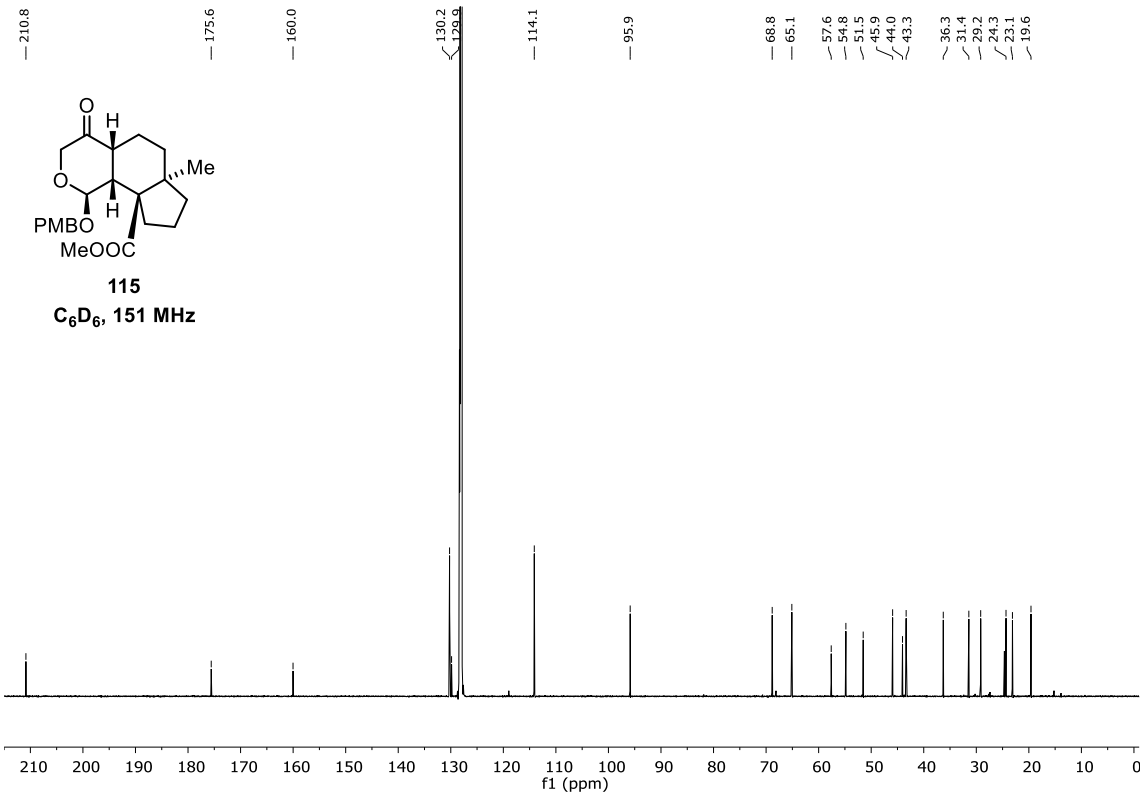
C_6D_6, 151MHz



115

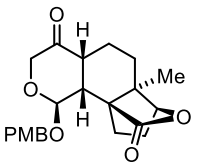
C_6D_6, 600 MHz



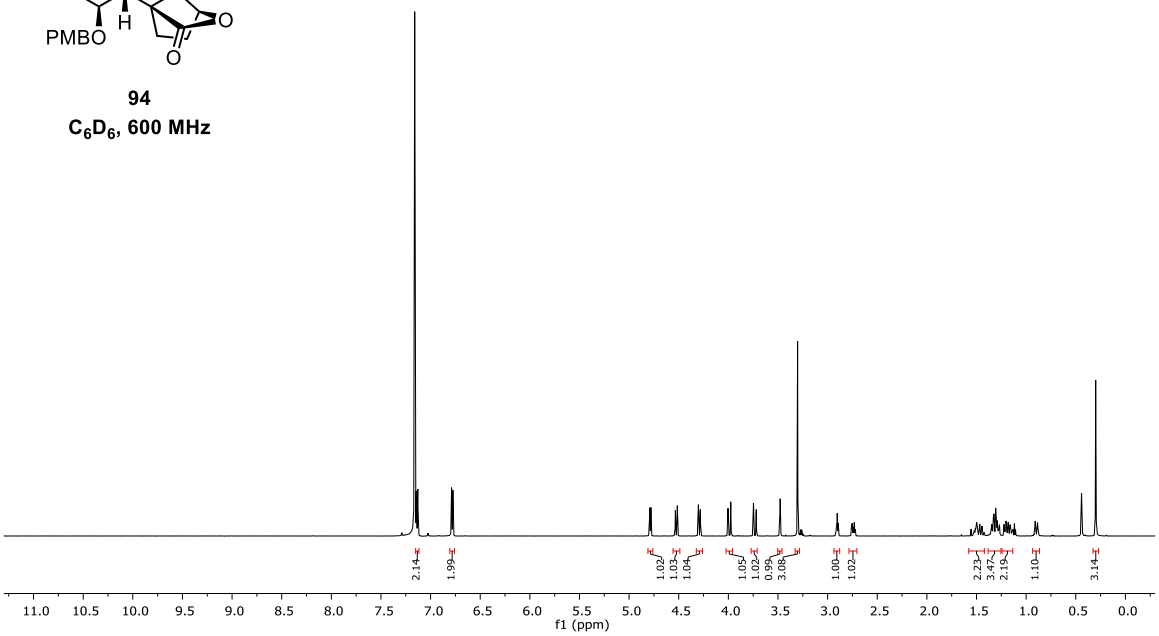


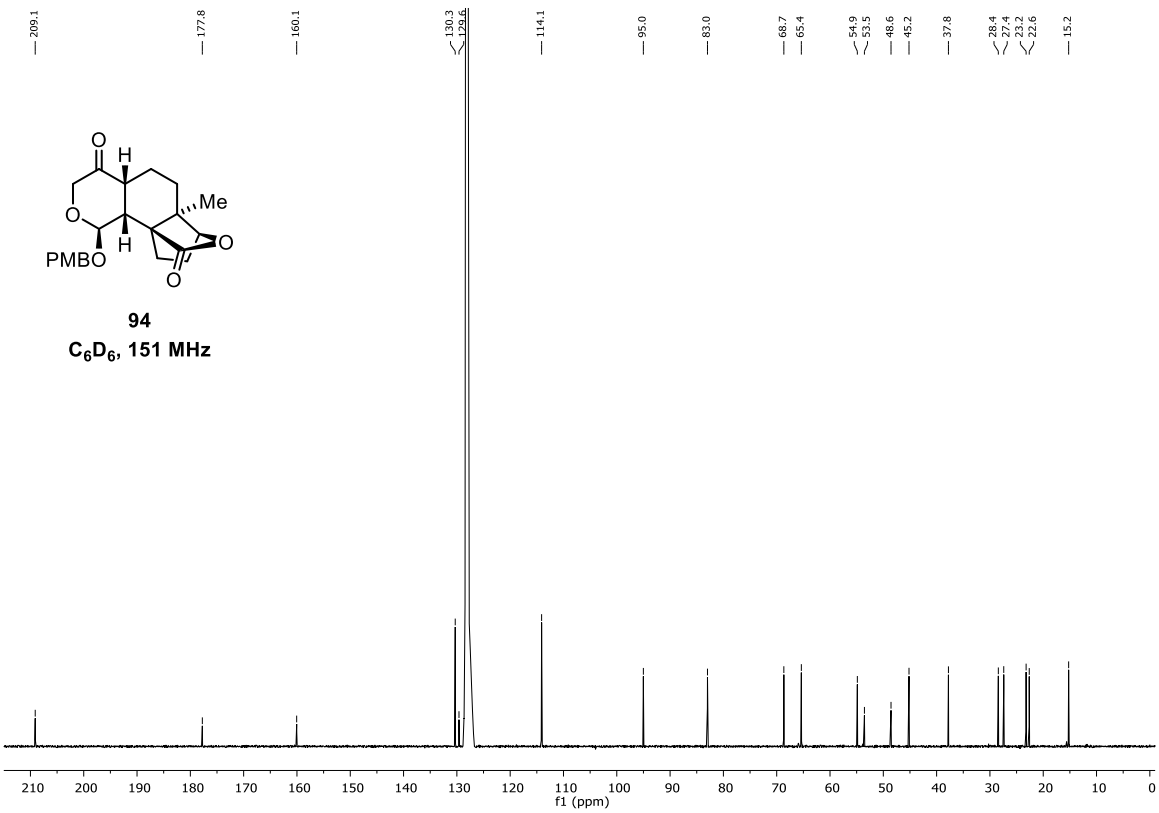
115

C_6D_6, 151 MHz

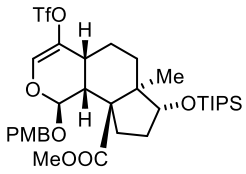


94
C_6D_6, 600 MHz



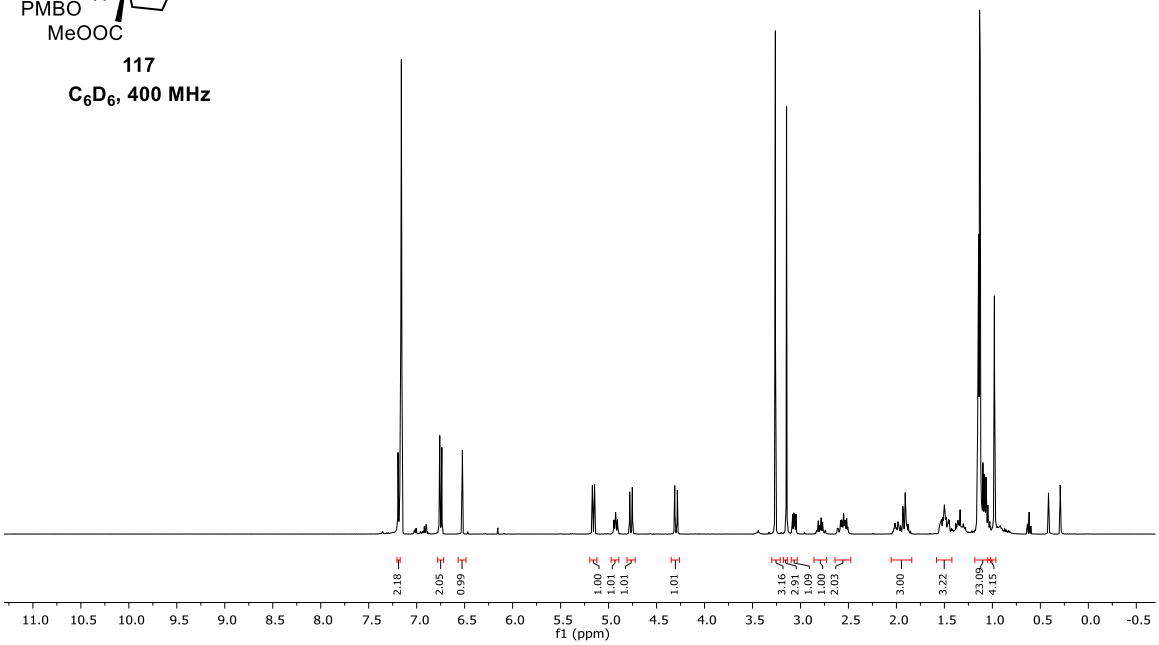


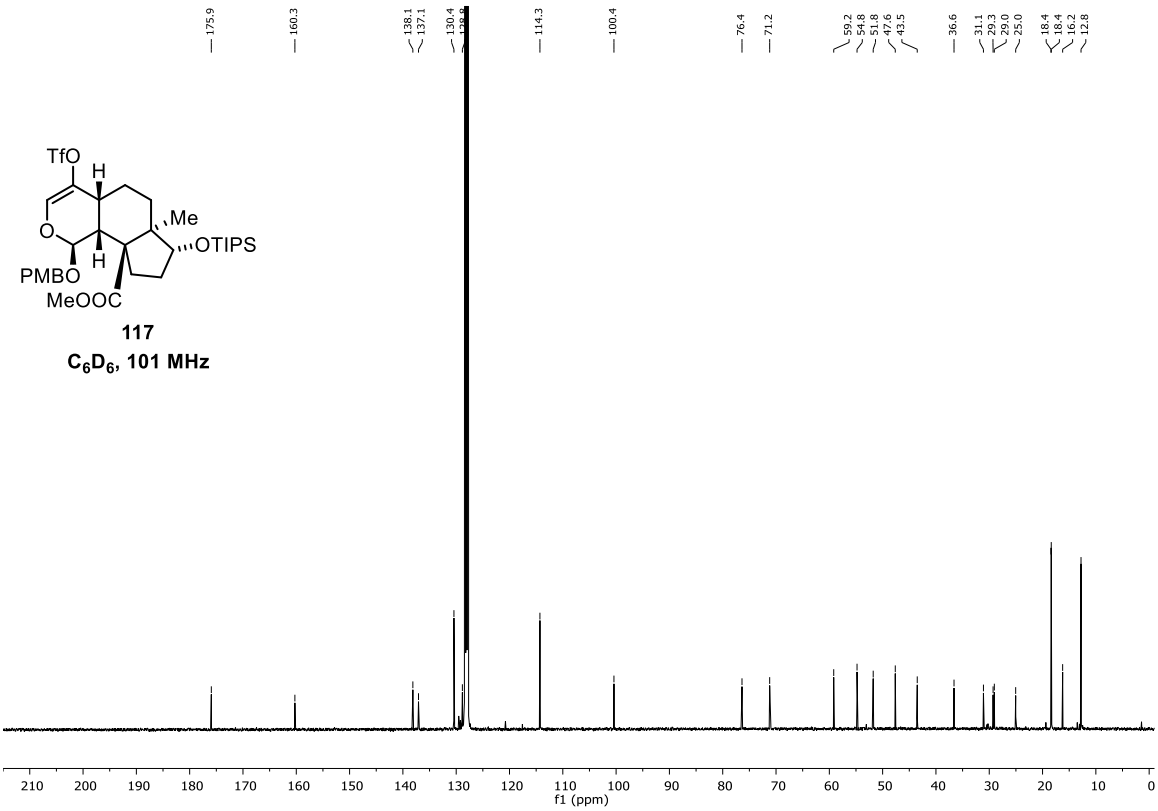
94
C_6D_6, 151 MHz



117

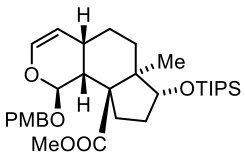
C_6D_6, 400 MHz



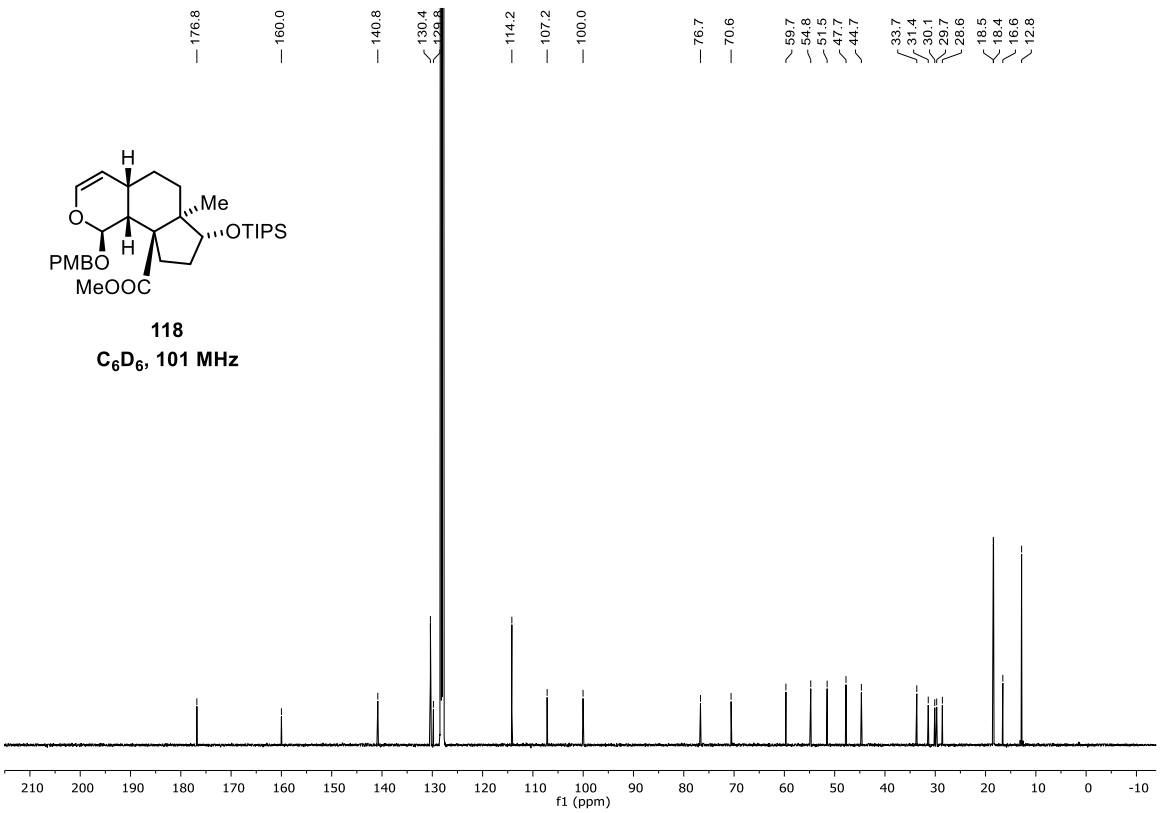


117

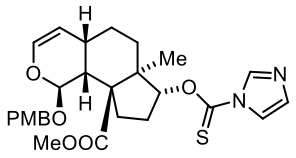
C_6D_6, 101 MHz



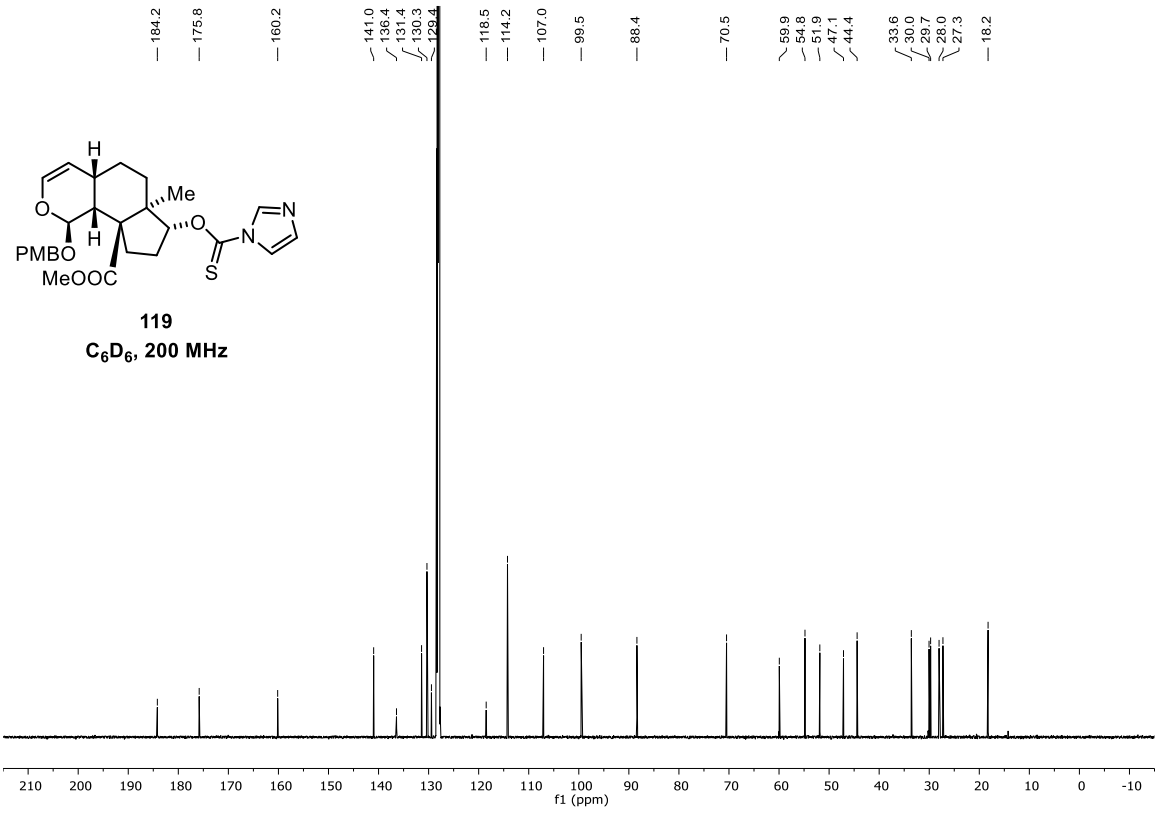
118
C_6D_6, 400 MHz



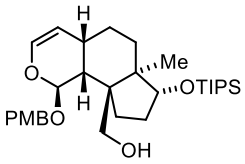
118
C_6D_6, 101 MHz



119
C_6D_6, 800 MHz

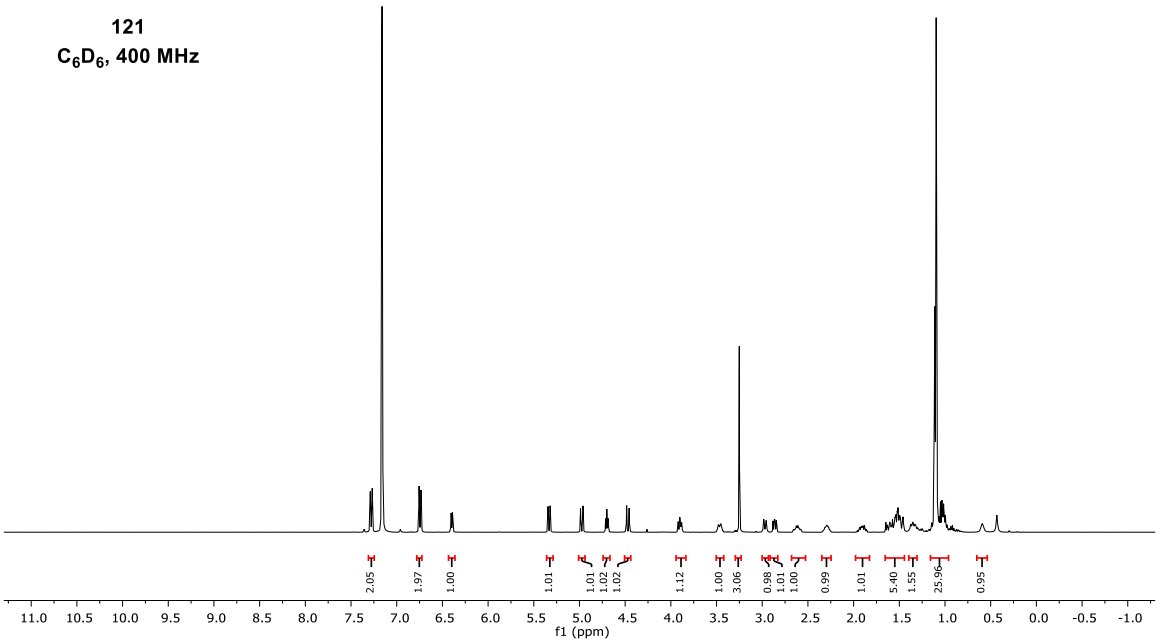


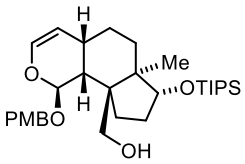
119
C_6D_6, 200 MHz



121

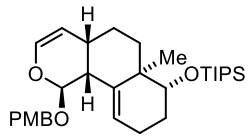
C_6D_6, 400 MHz



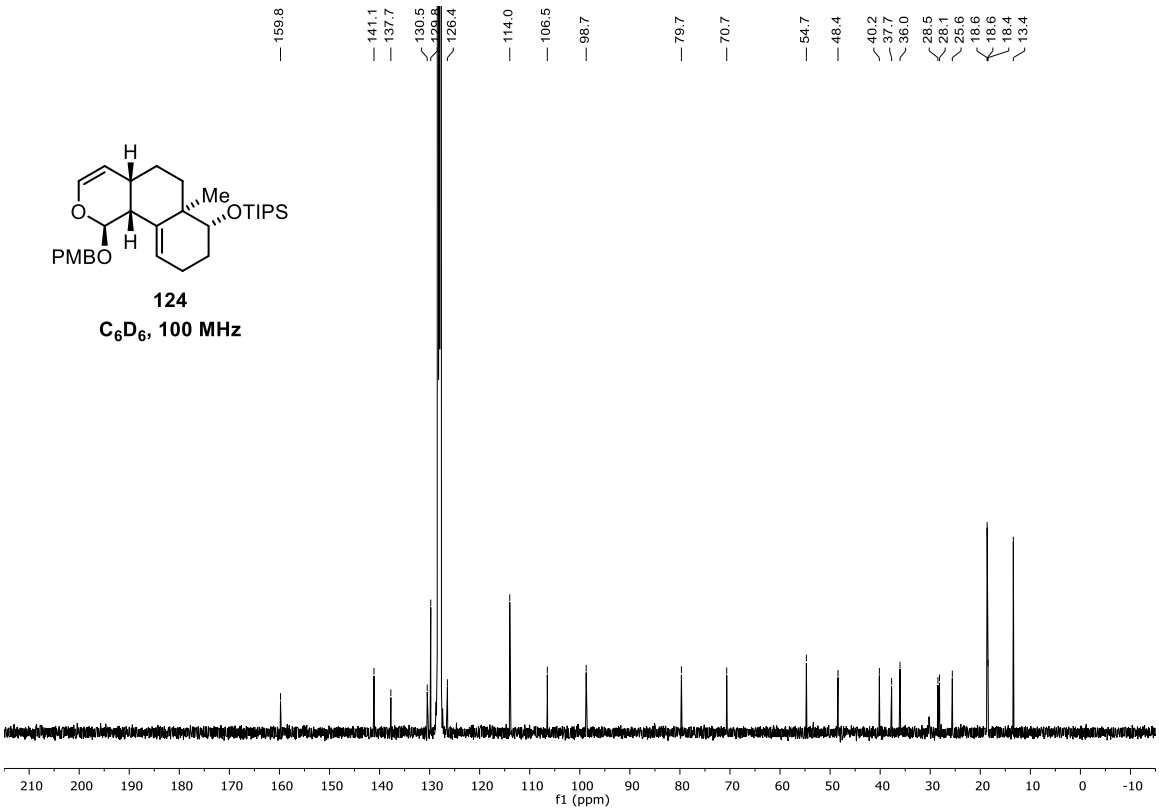


121

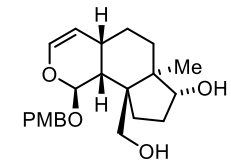
C_6D_6, 100 MHz



124
C_6D_6, 400 MHz

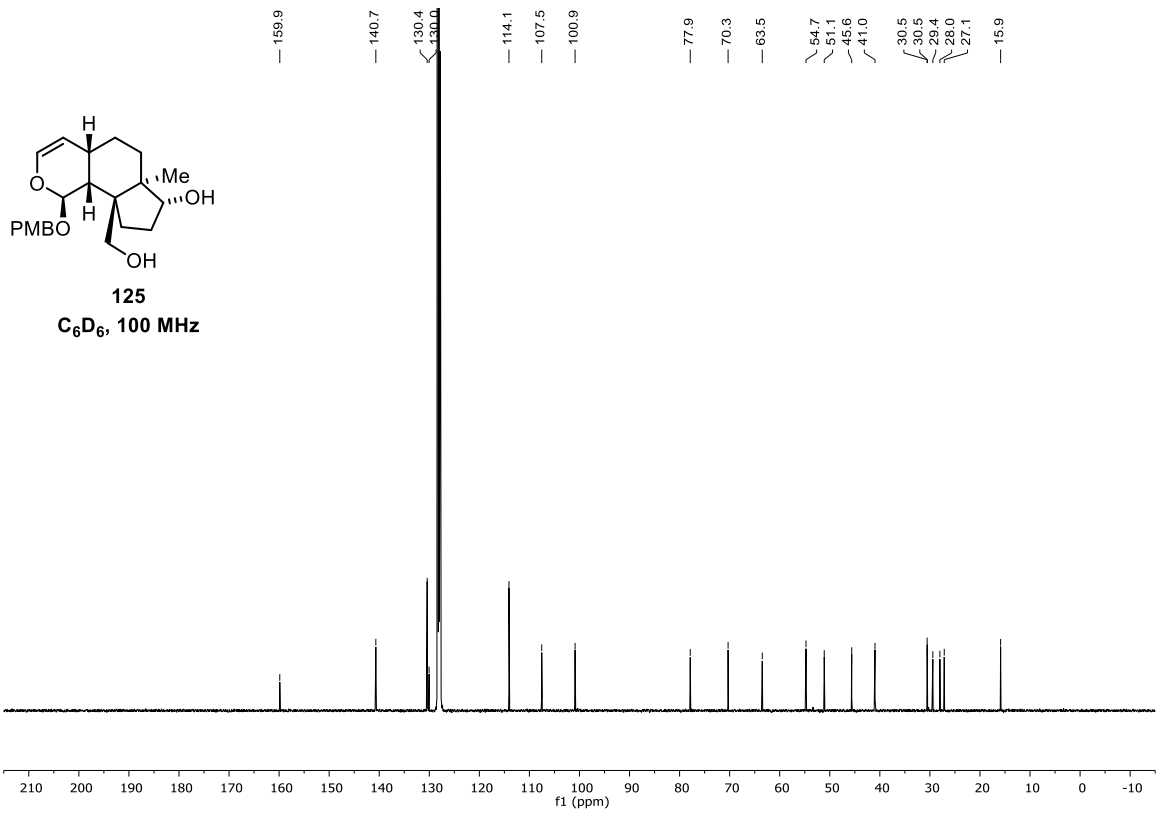


124
C_6D_6, 100 MHz



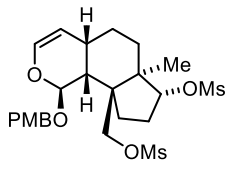
125

C_6D_6, 400 MHz



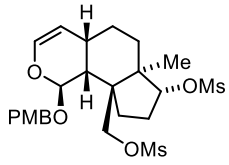
125

C_6D_6, 100 MHz



126

C_6D_6, 400 MHz

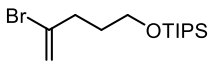


126

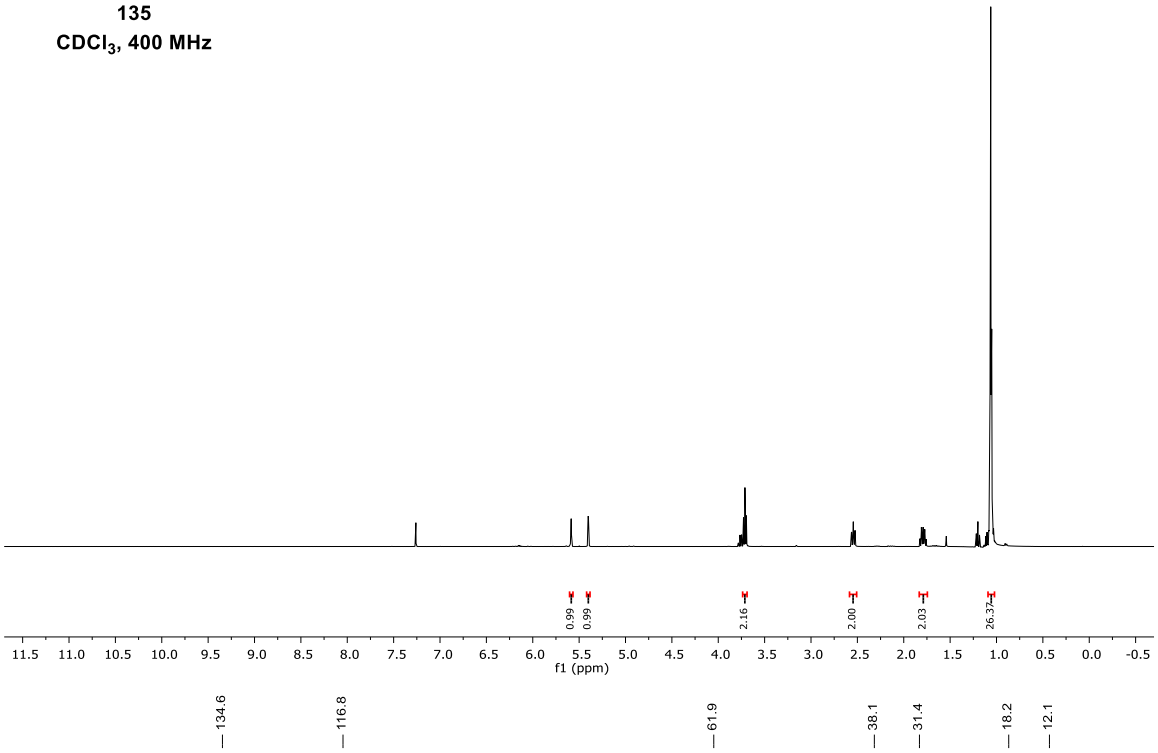
C_6D_6, 100 MHz

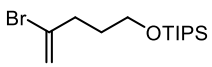
129
C_6D_6, 800 MHz

129
C_6D_6, 200 MHz

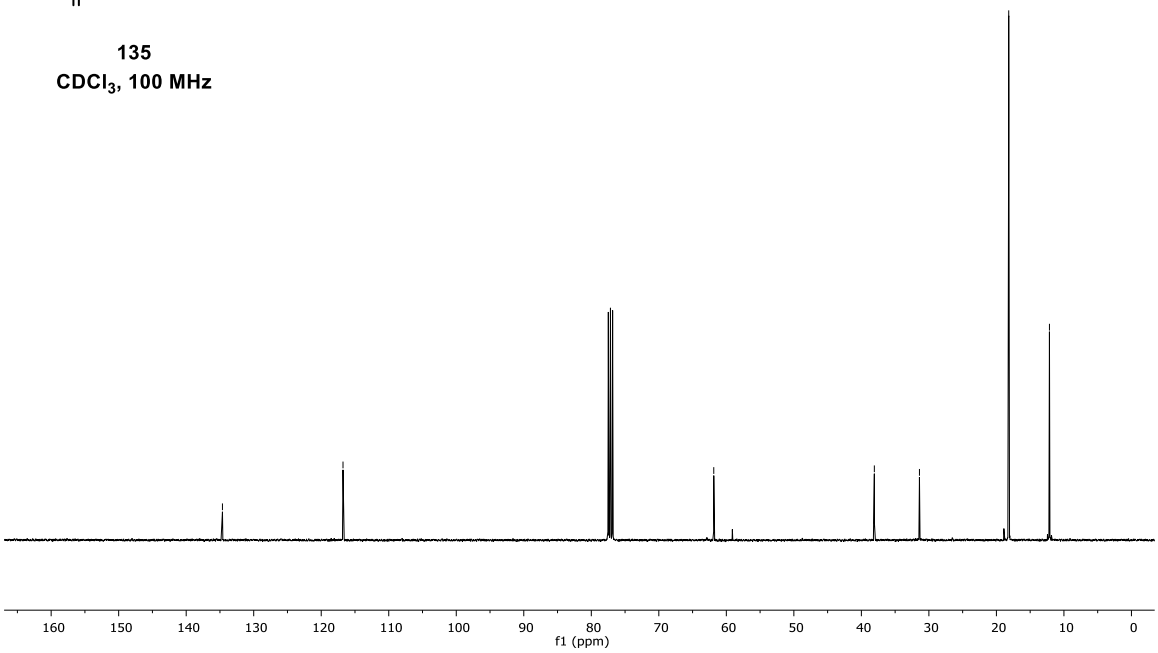


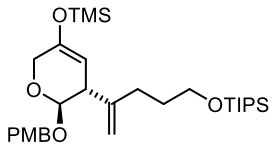
135
$CDCl_3$, 400 MHz



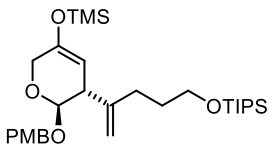


135
$CDCl_3$, 100 MHz

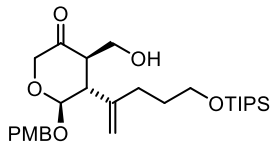




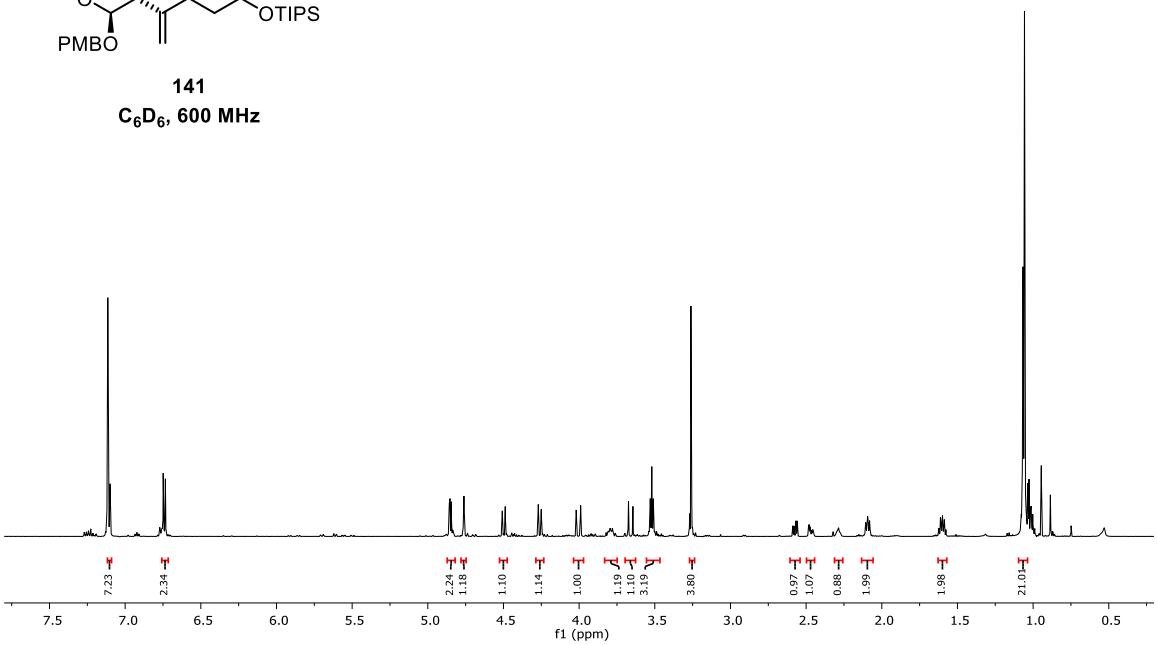
139
C_6D_6, 400 MHz

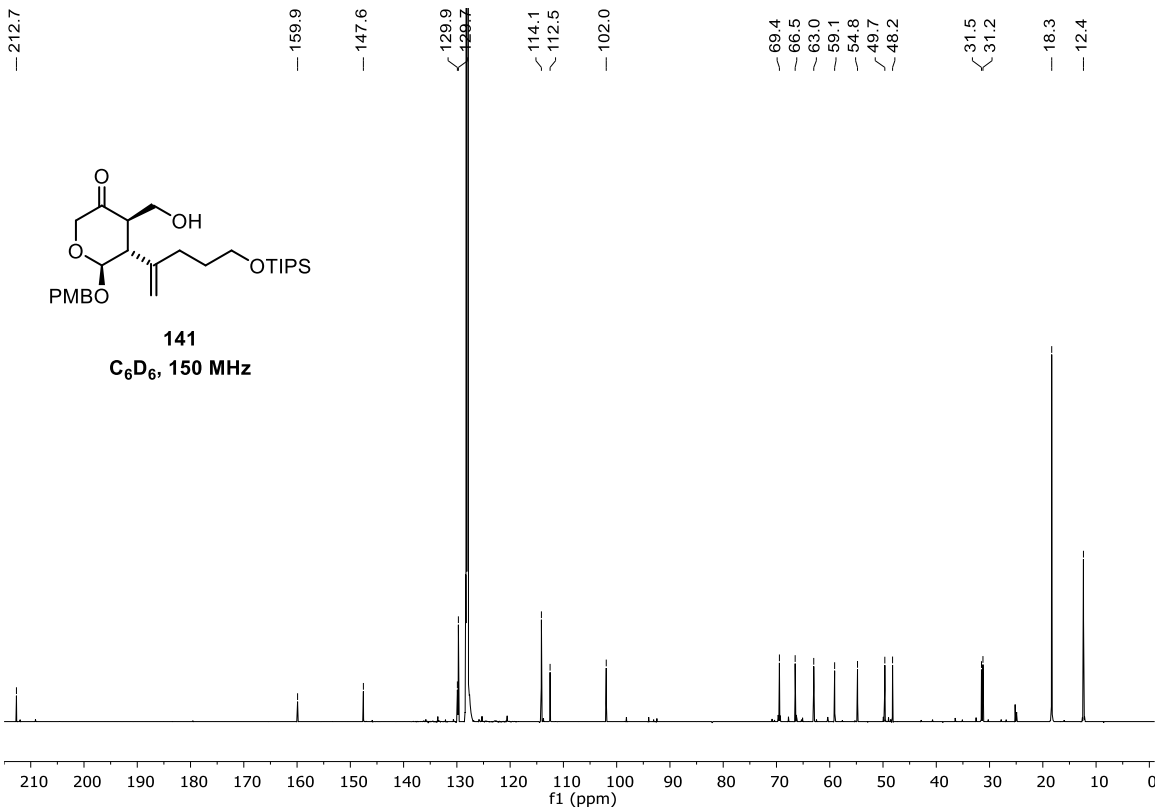


139
C_6D_6, 100 MHz

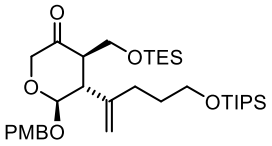


141
C_6D_6, 600 MHz

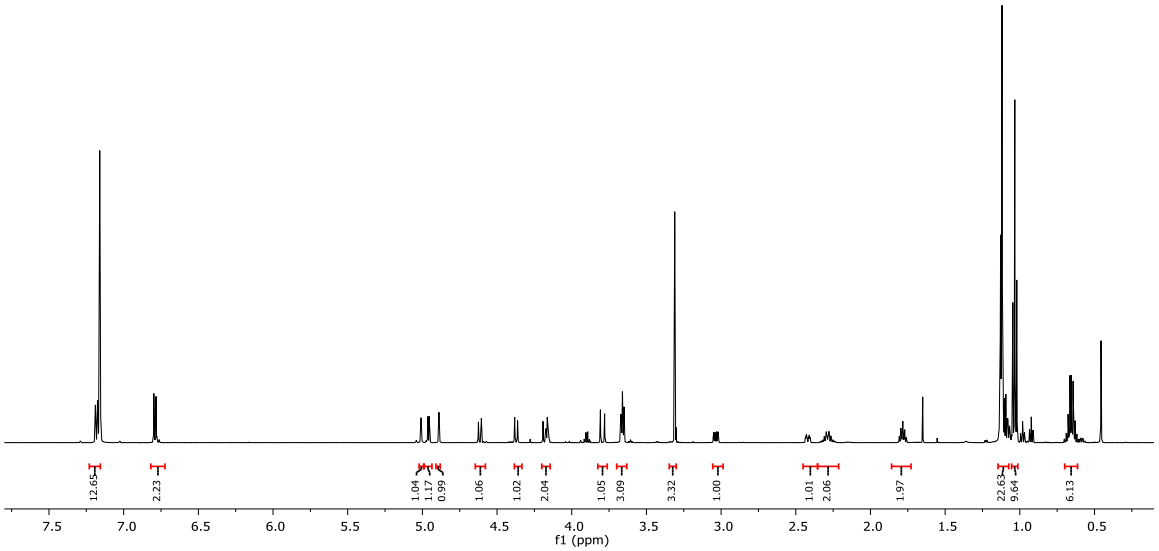


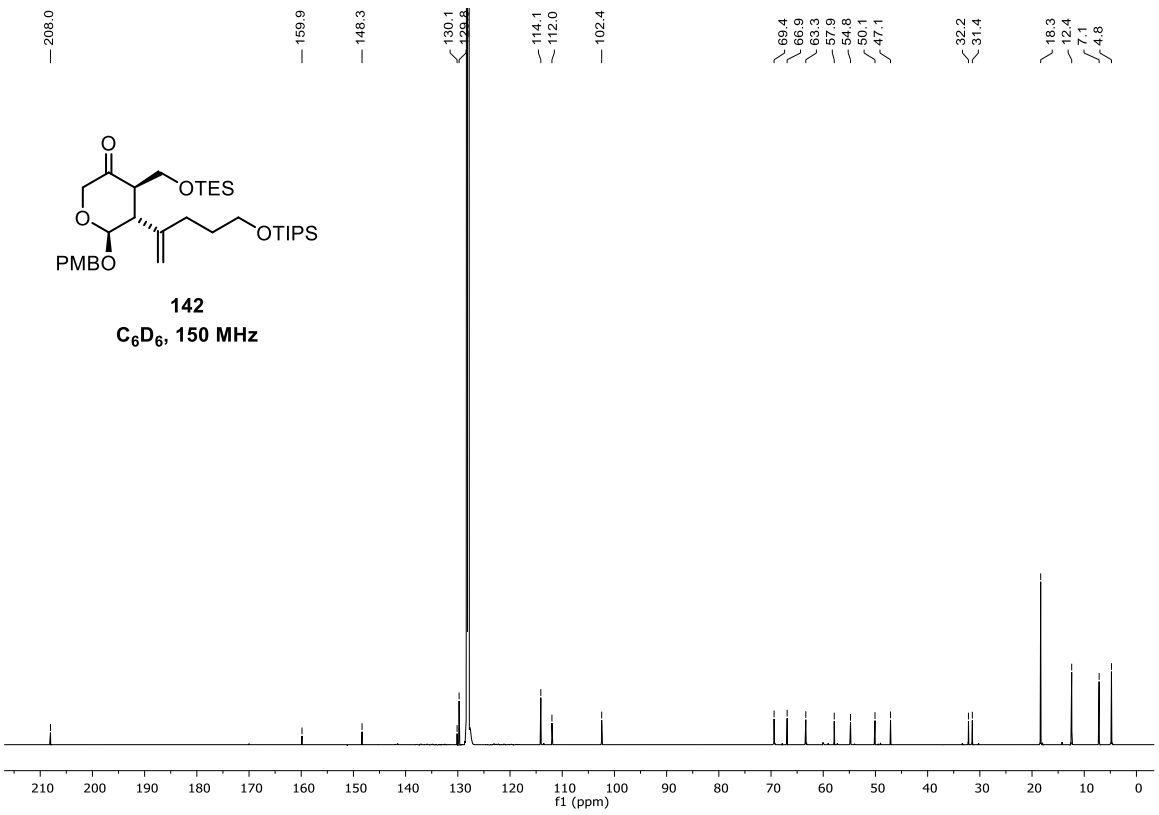


141
C_6D_6, 150 MHz

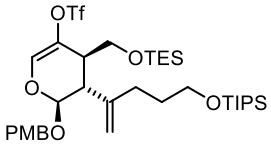


142
C_6D_6, 600 MHz

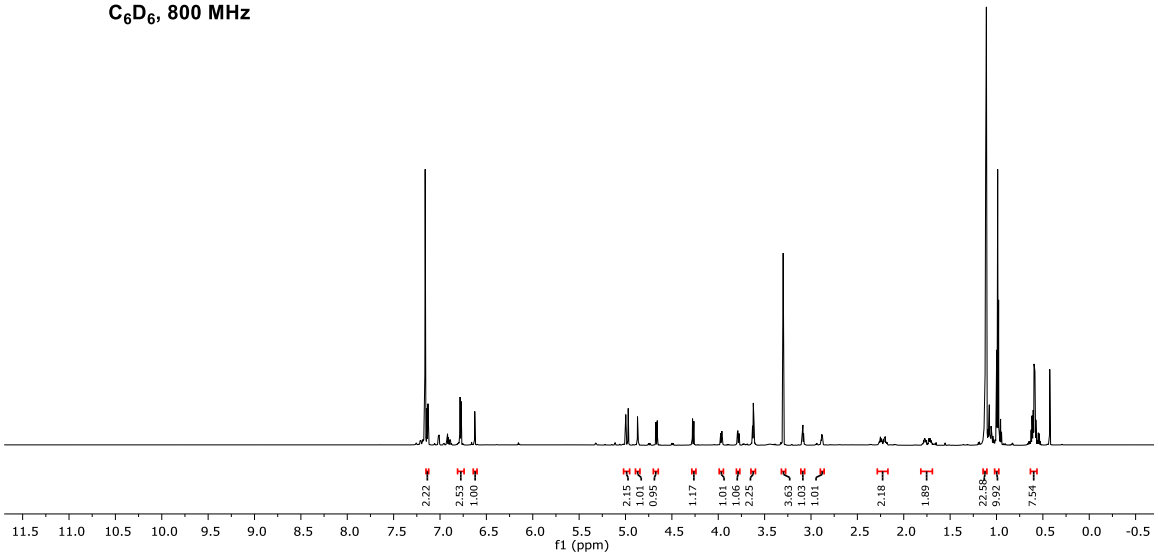


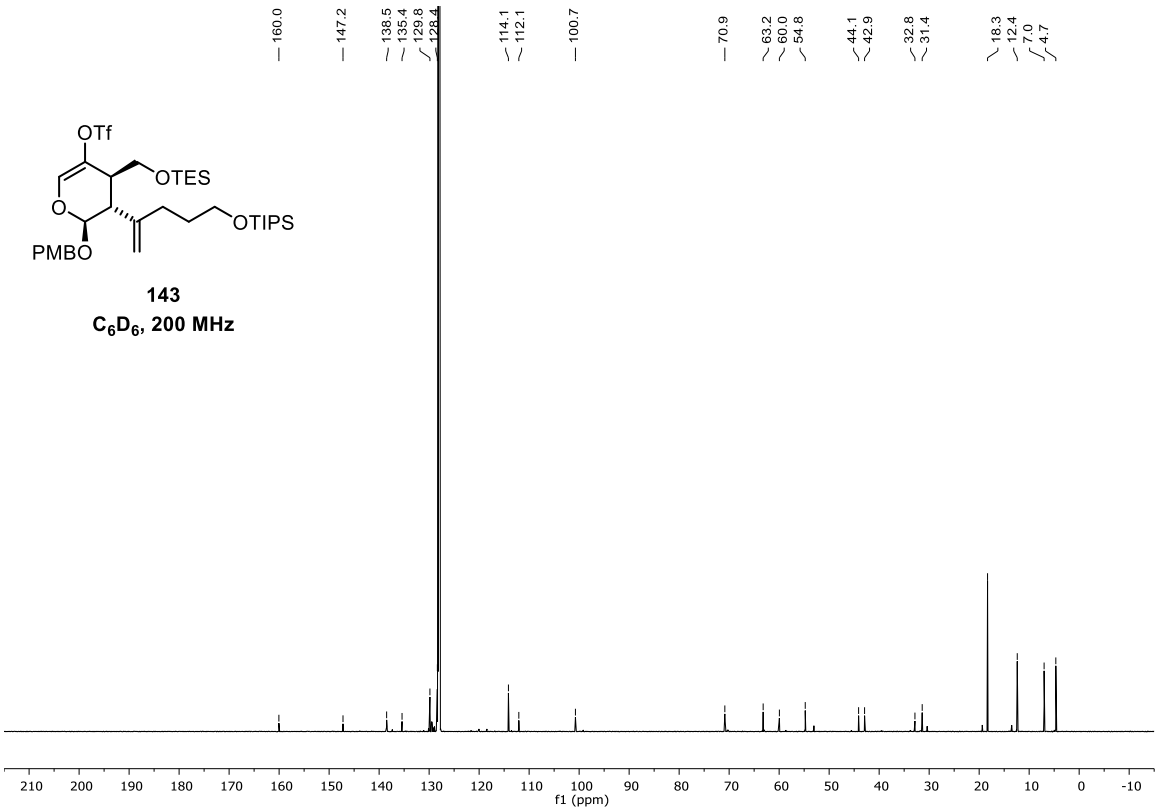


142
C_6D_6, 150 MHz

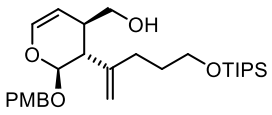


143
C_6D_6, 800 MHz

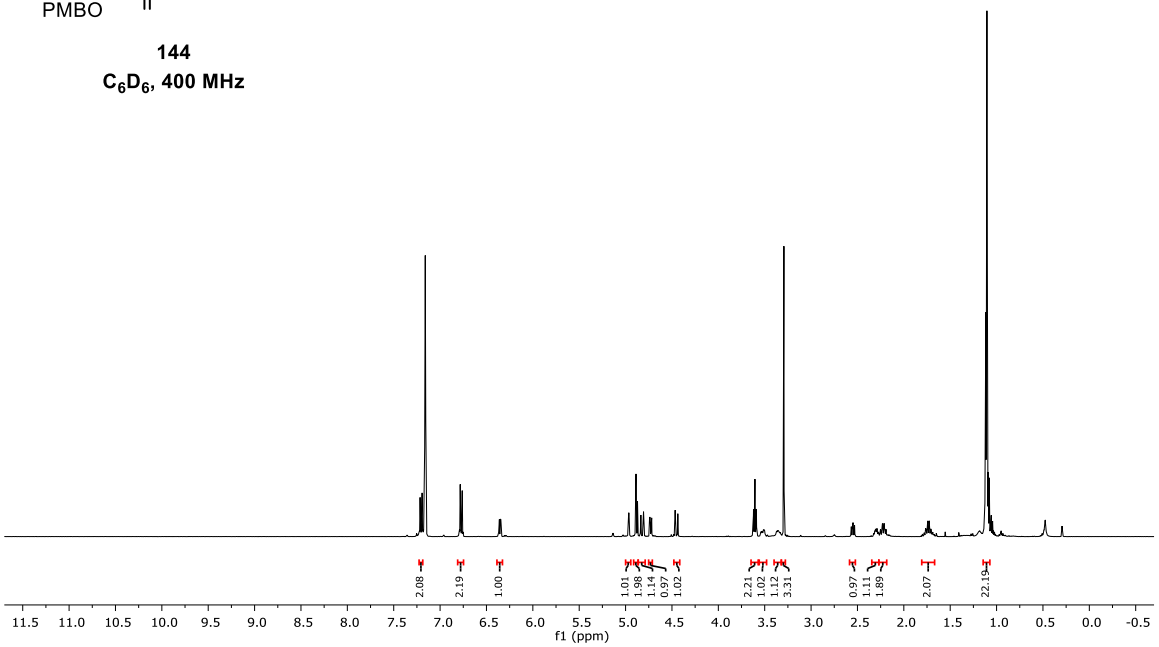


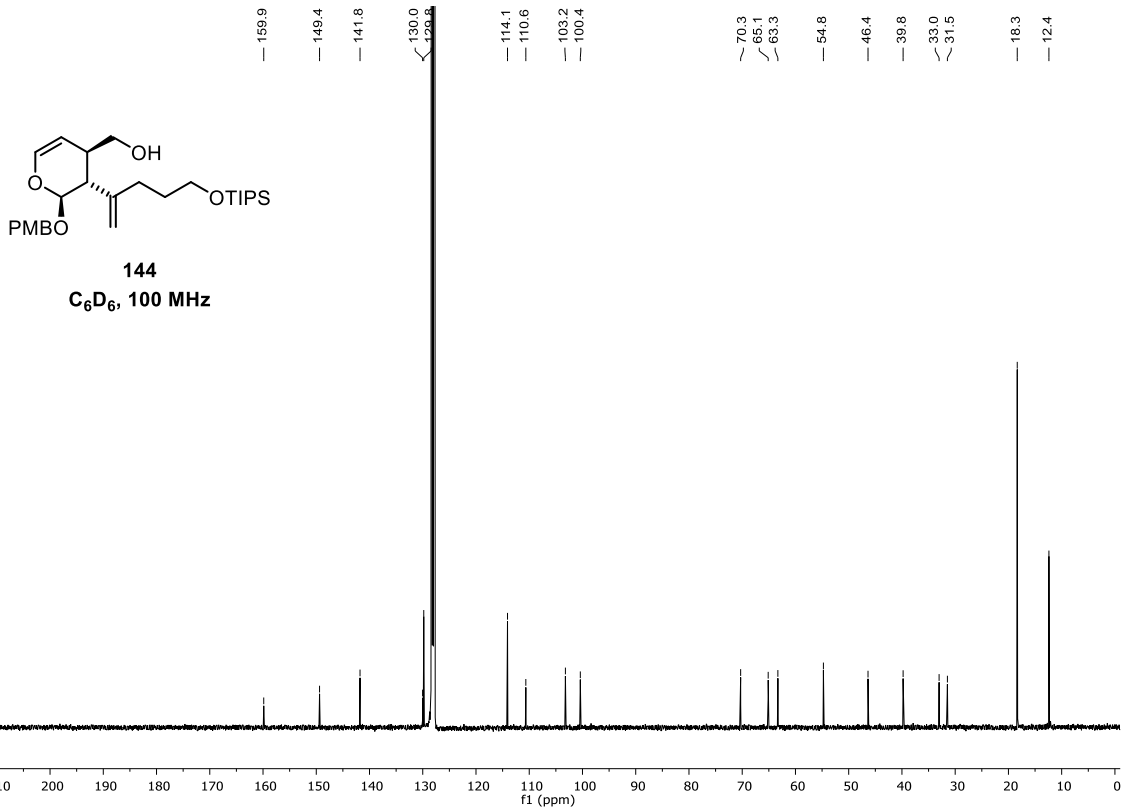


143
C_6D_6, 200 MHz

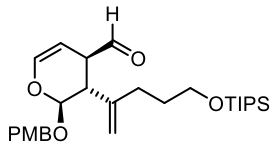


144
C_6D_6, 400 MHz

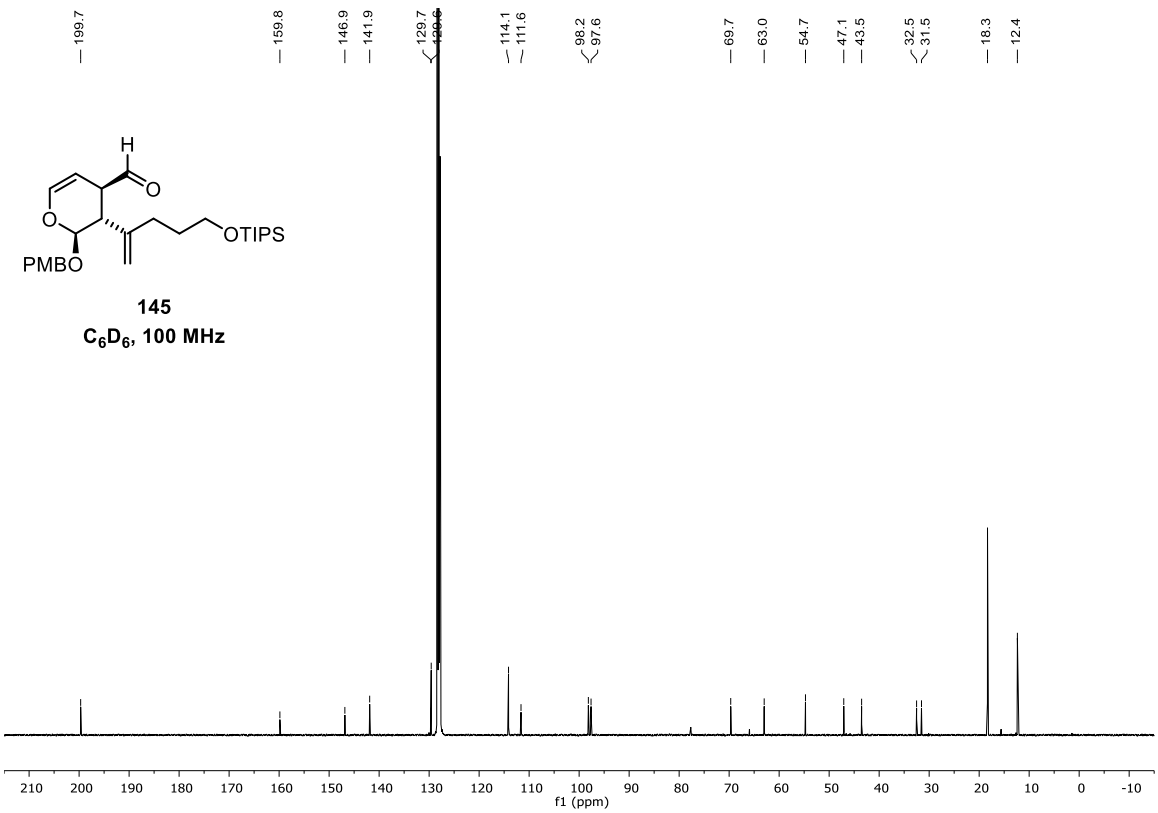




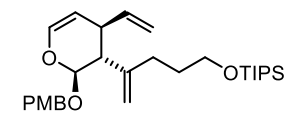
144
C_6D_6, 100 MHz



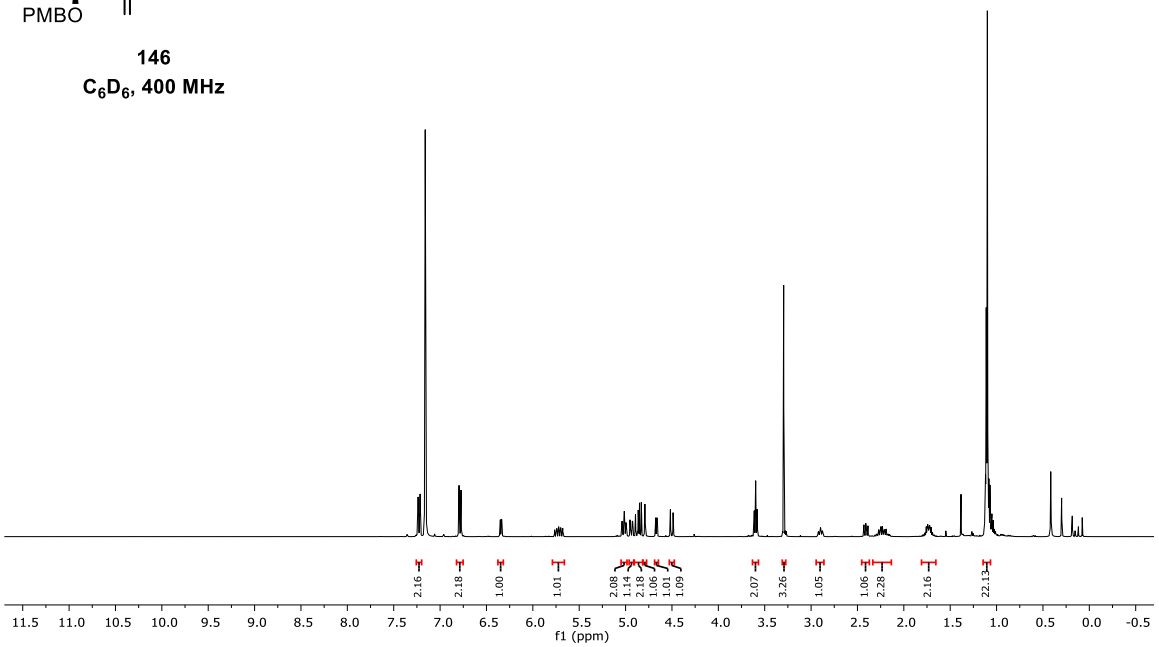
145
C_6D_6, 400 MHz

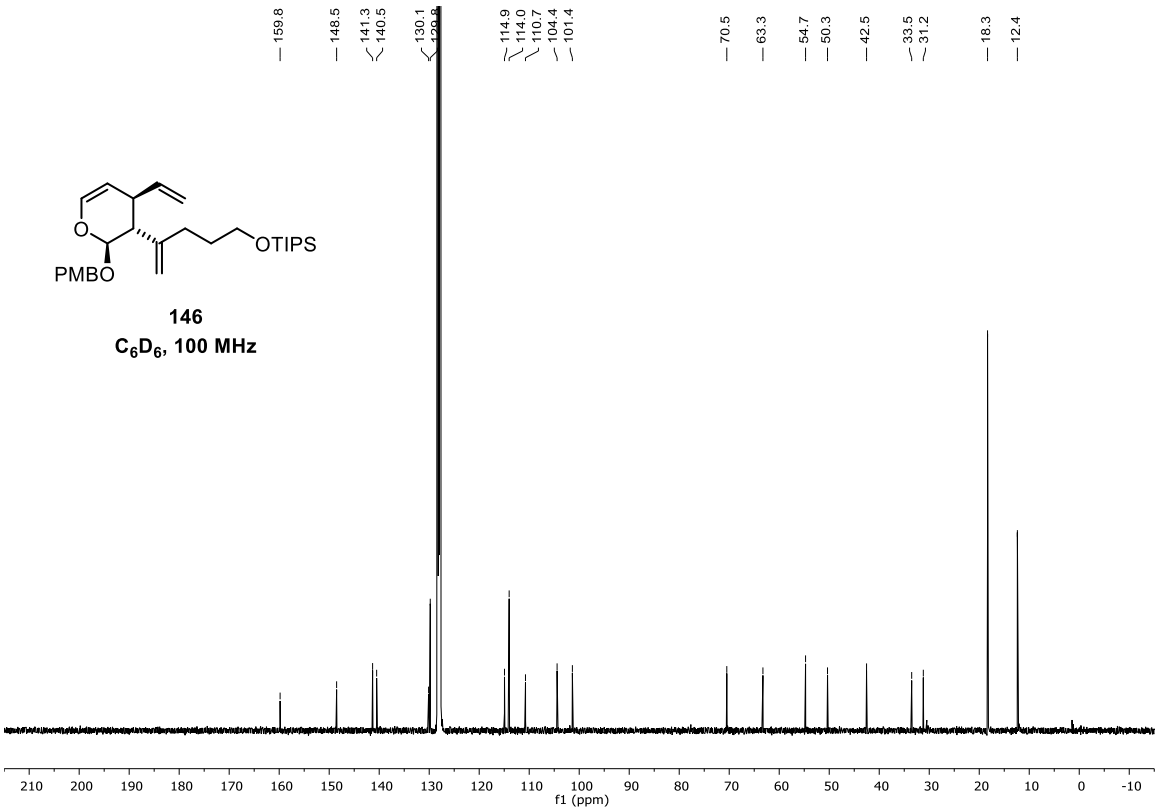


145
C_6D_6, 100 MHz

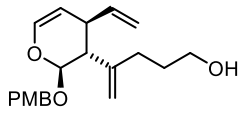


146
C_6D_6, 400 MHz

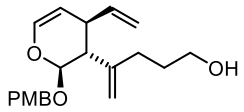




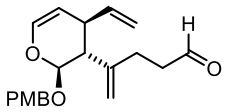
146
C_6D_6, 100 MHz



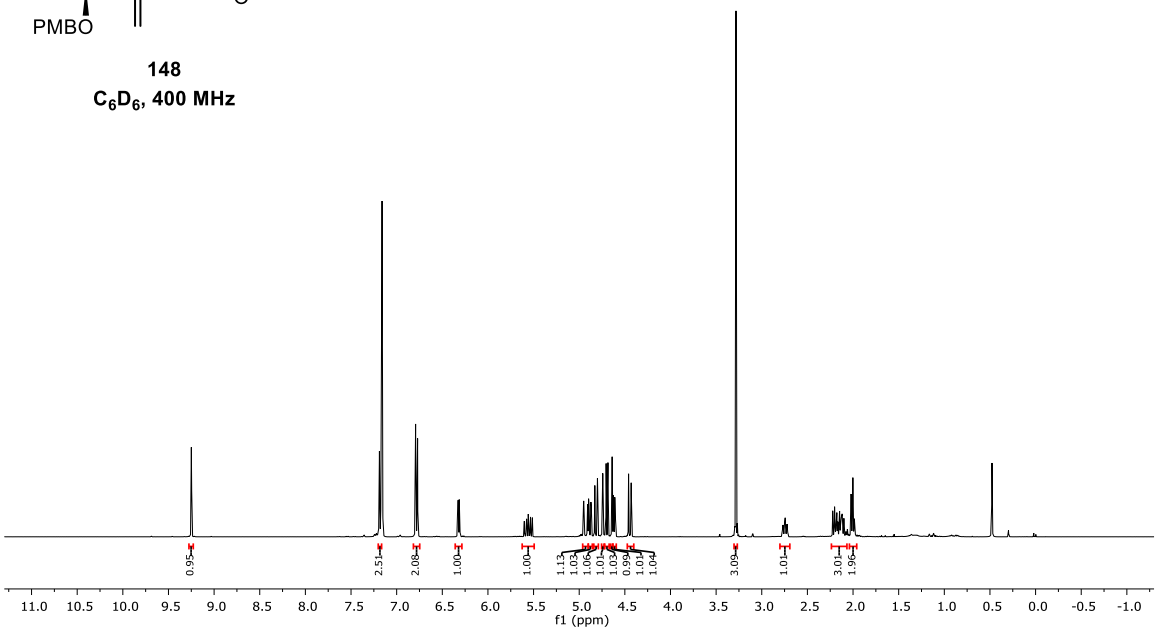
147
C_6D_6, 800 MHz

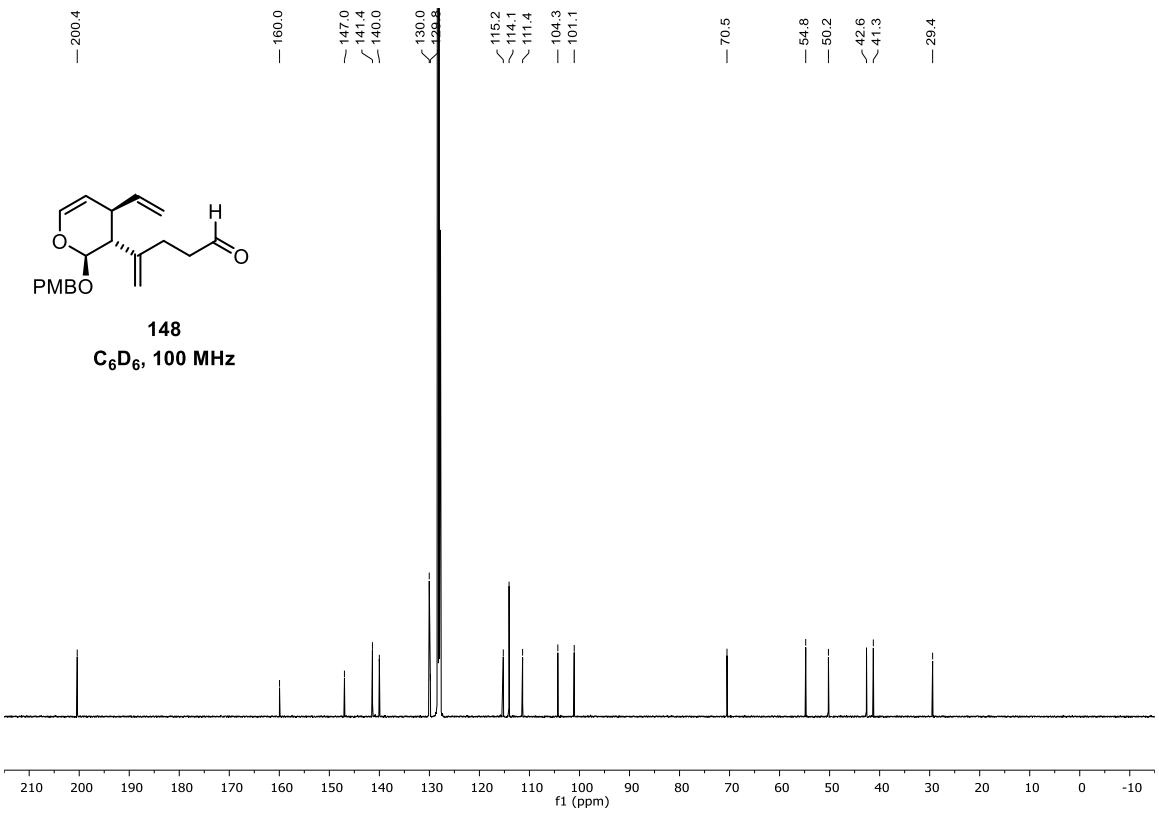


147
C_6D_6, 200 MHz

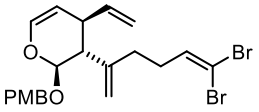


148
C_6D_6, 400 MHz

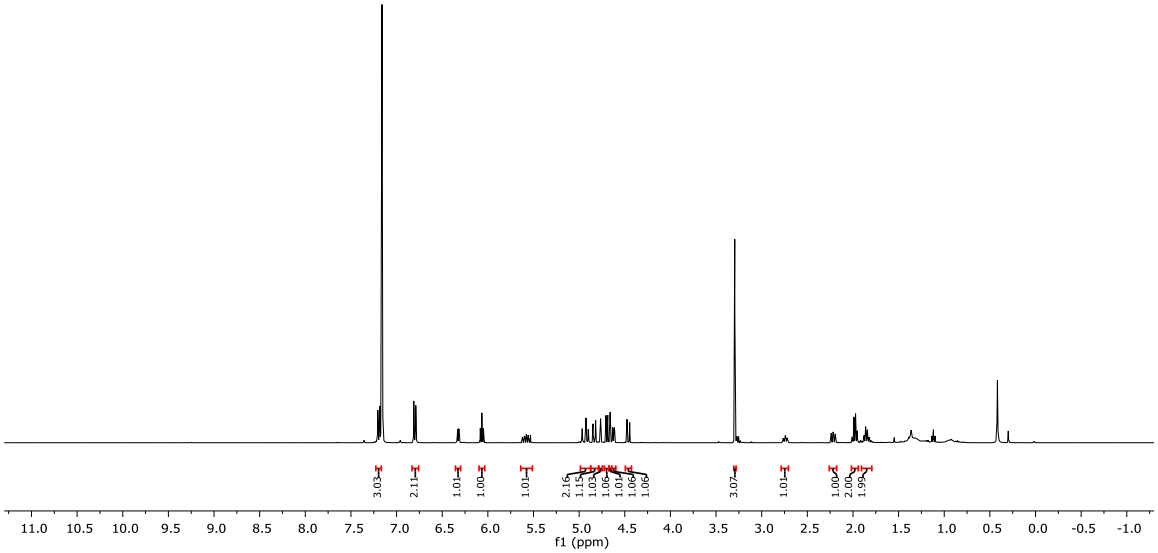


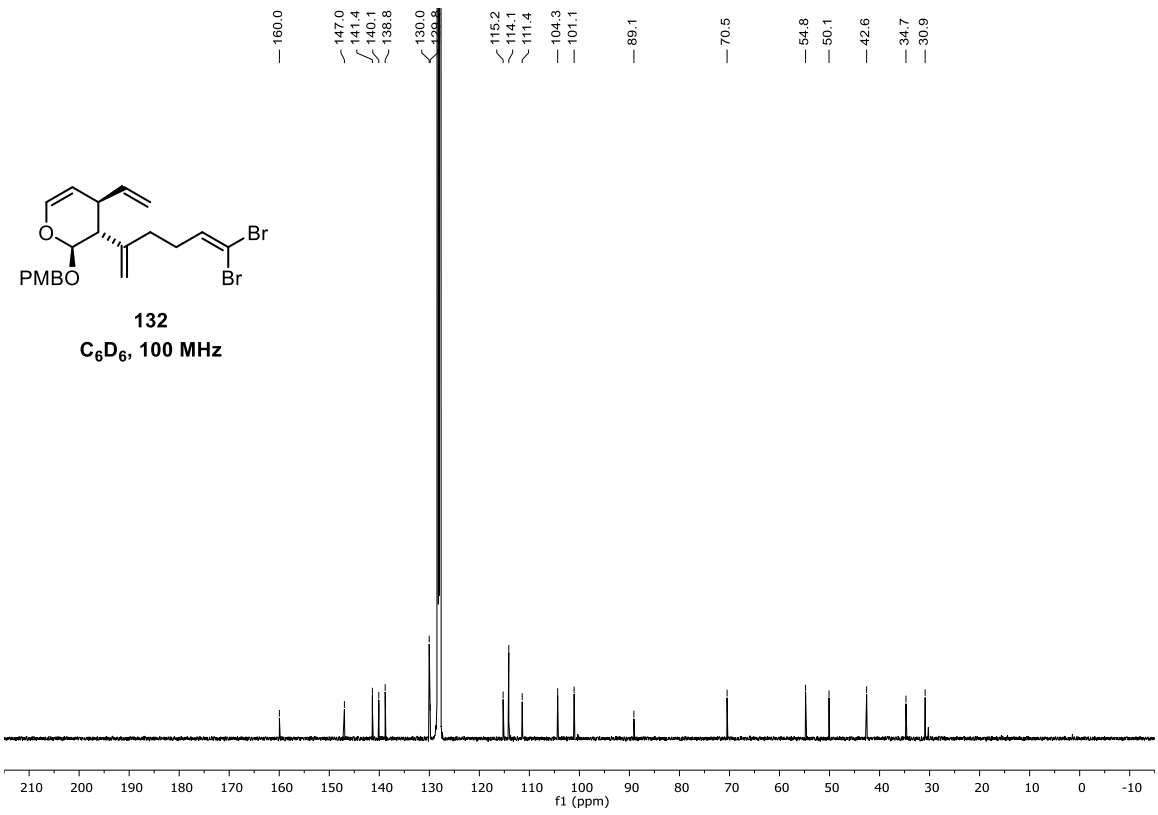


148
C_6D_6, 100 MHz

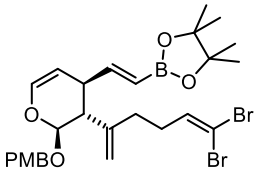


132
C_6D_6, 400 MHz

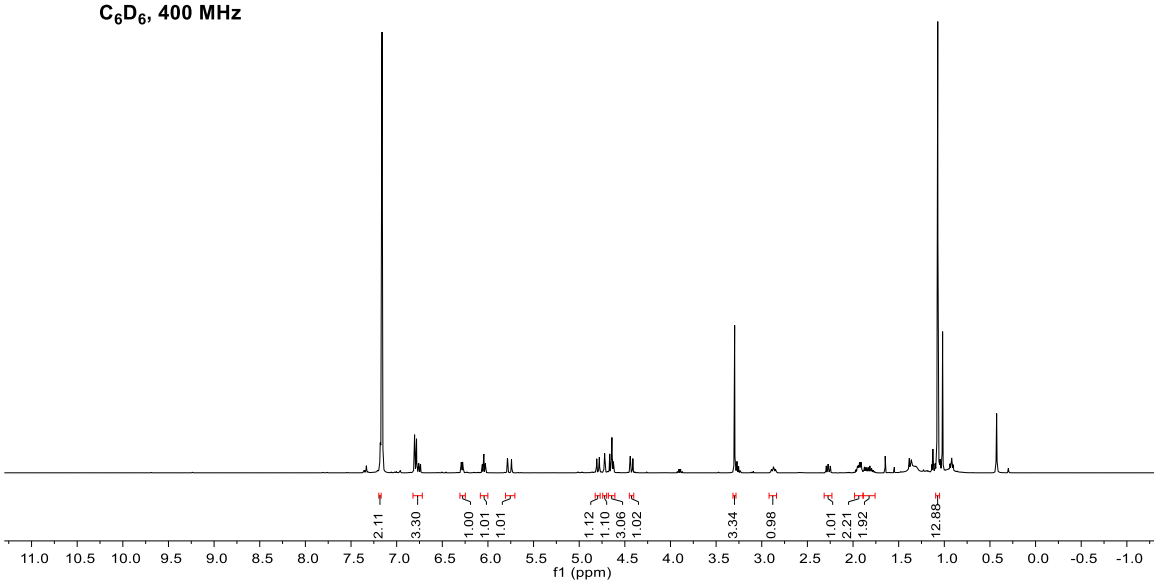


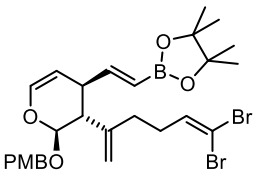


132
C_6D_6, 100 MHz

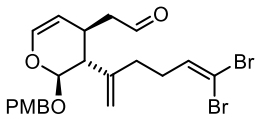


152
C_6D_6, 400 MHz

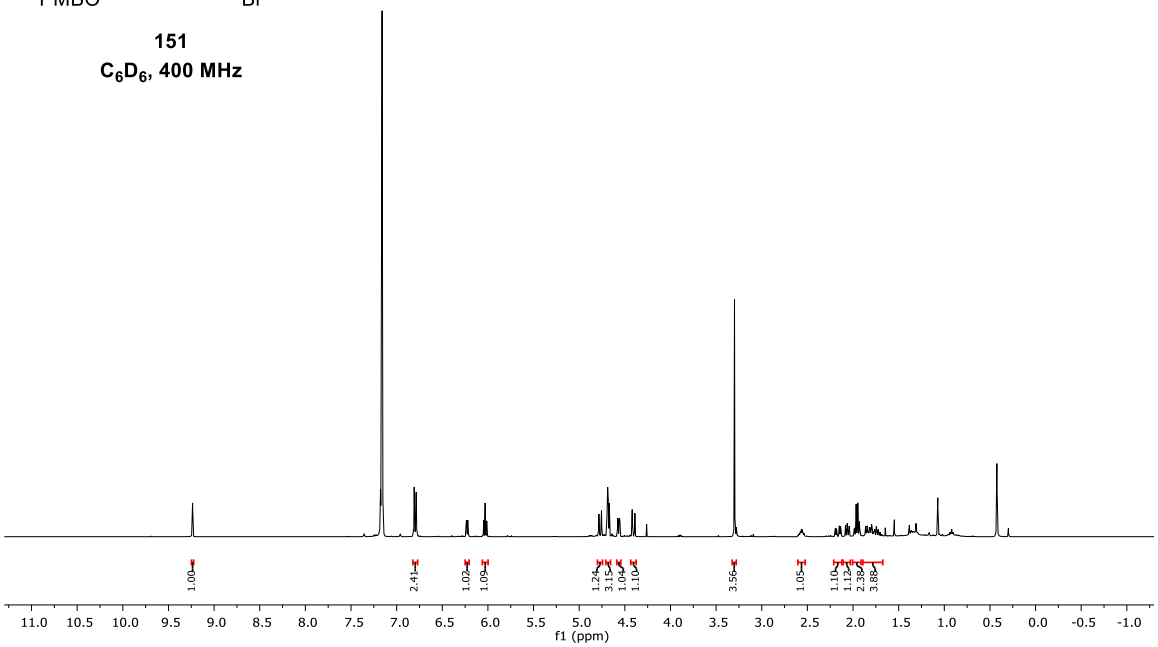


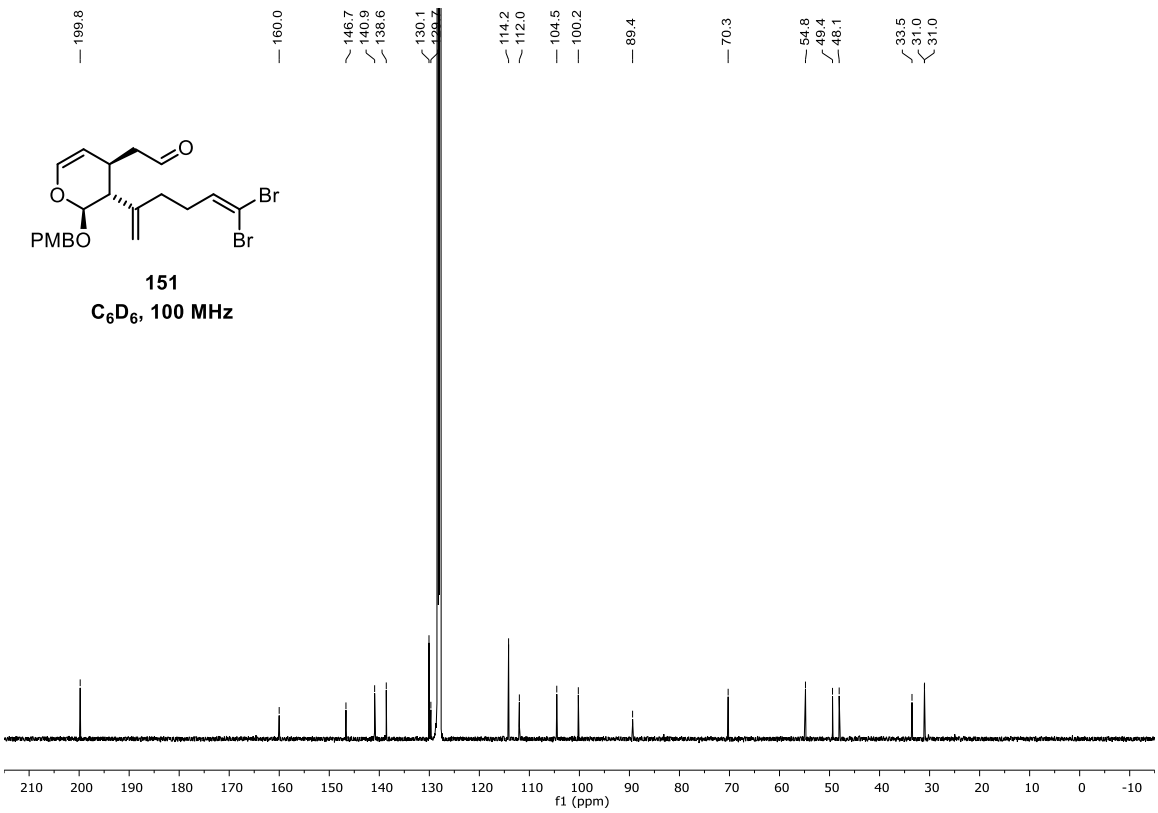


152
C_6D_6, 100 MHz

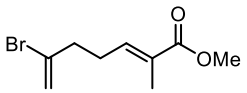


151
C_6D_6, 400 MHz

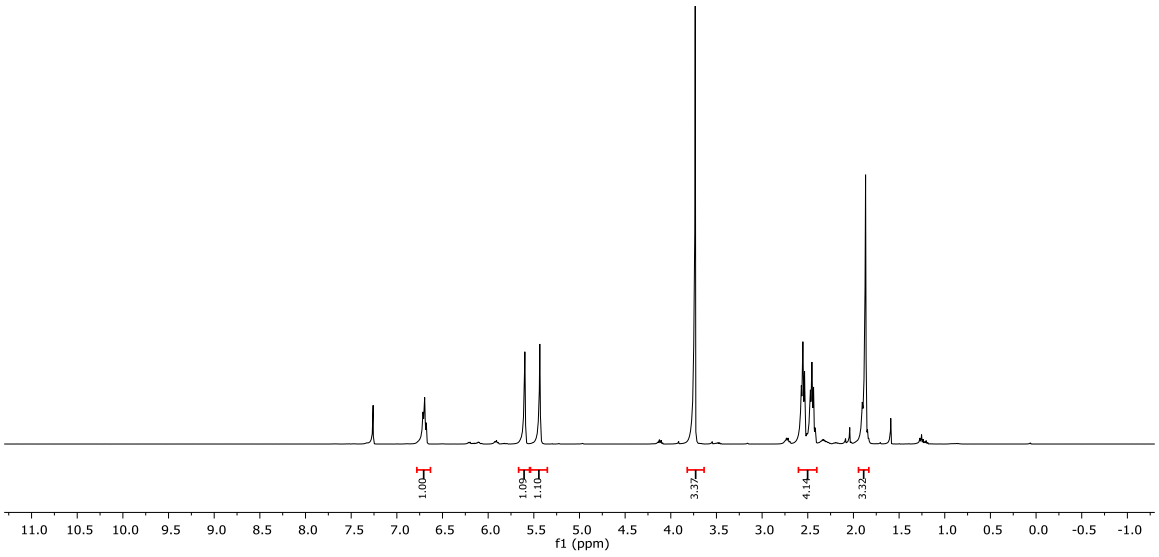


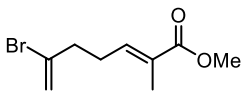


151
C_6D_6, 100 MHz

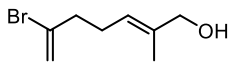


160
$CDCl_3$, 400 MHz

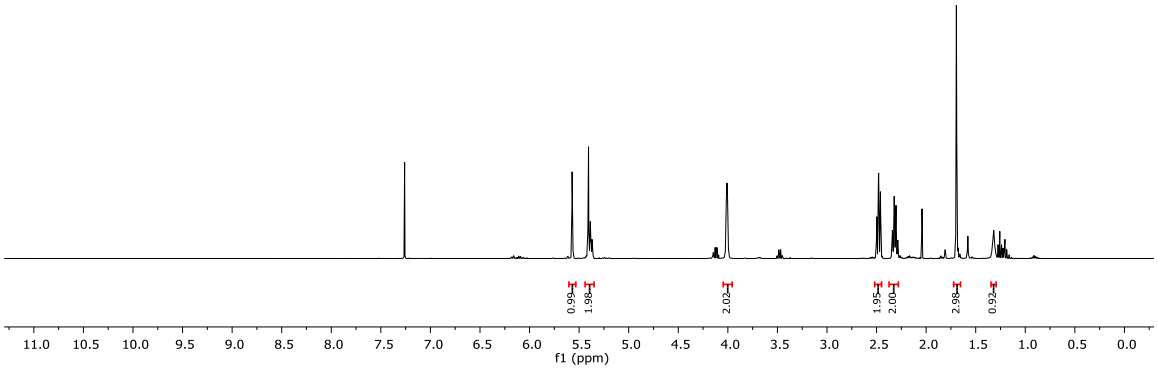




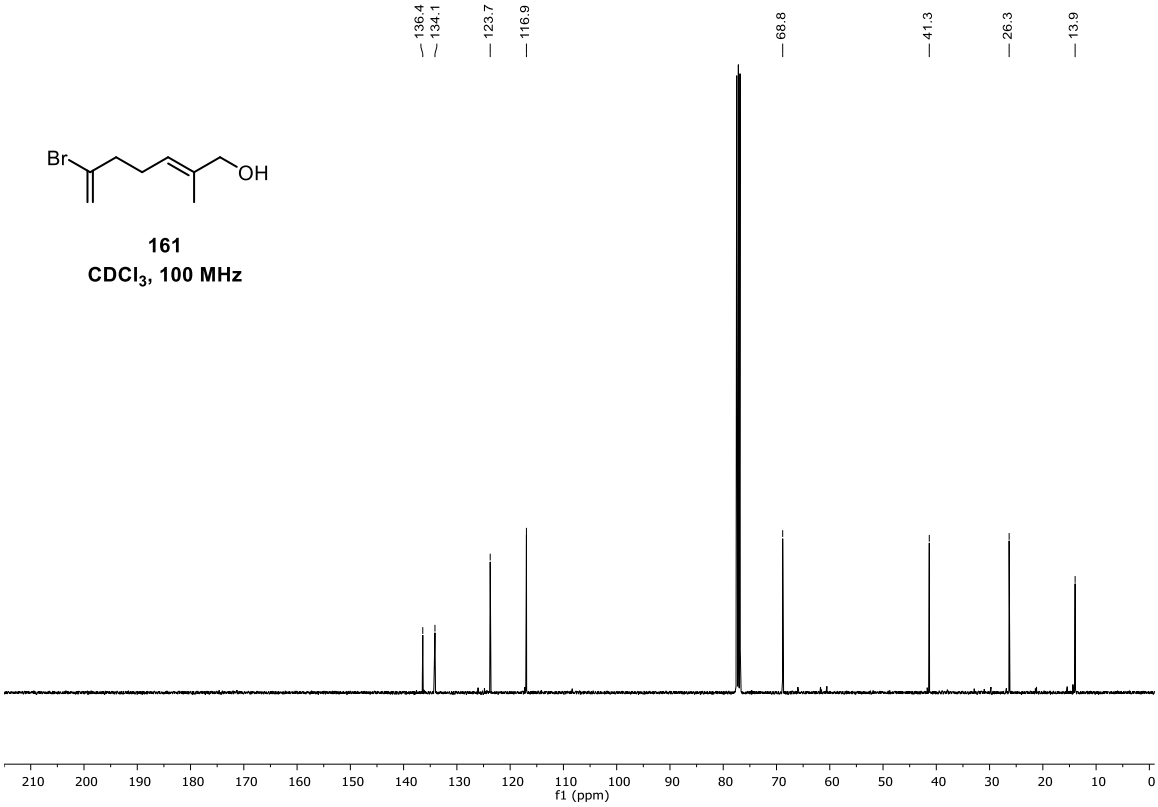
160
$CDCl_3$, 100 MHz

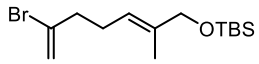


161
$CDCl_3$, 400 MHz

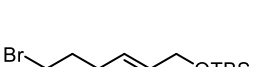


161
$CDCl_3$, 100 MHz

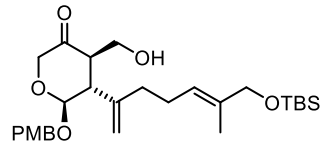




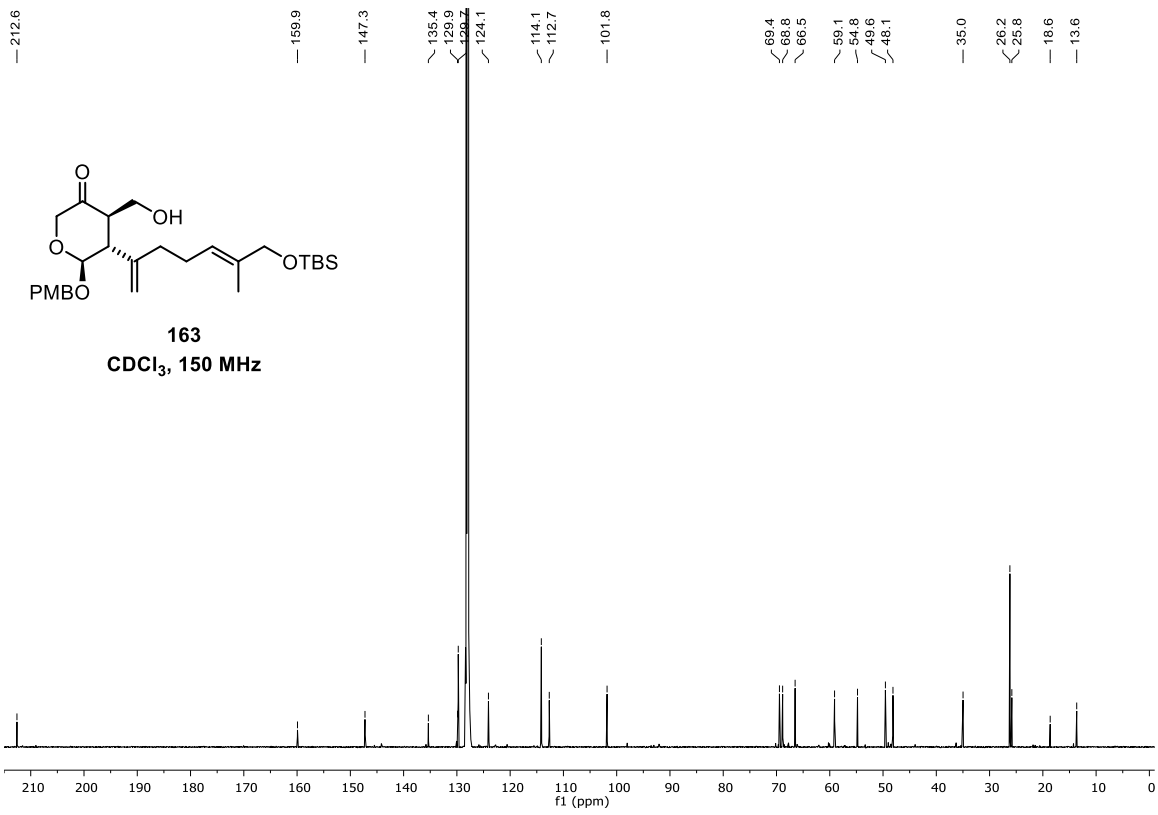
136
$CDCl_3$, 400 MHz



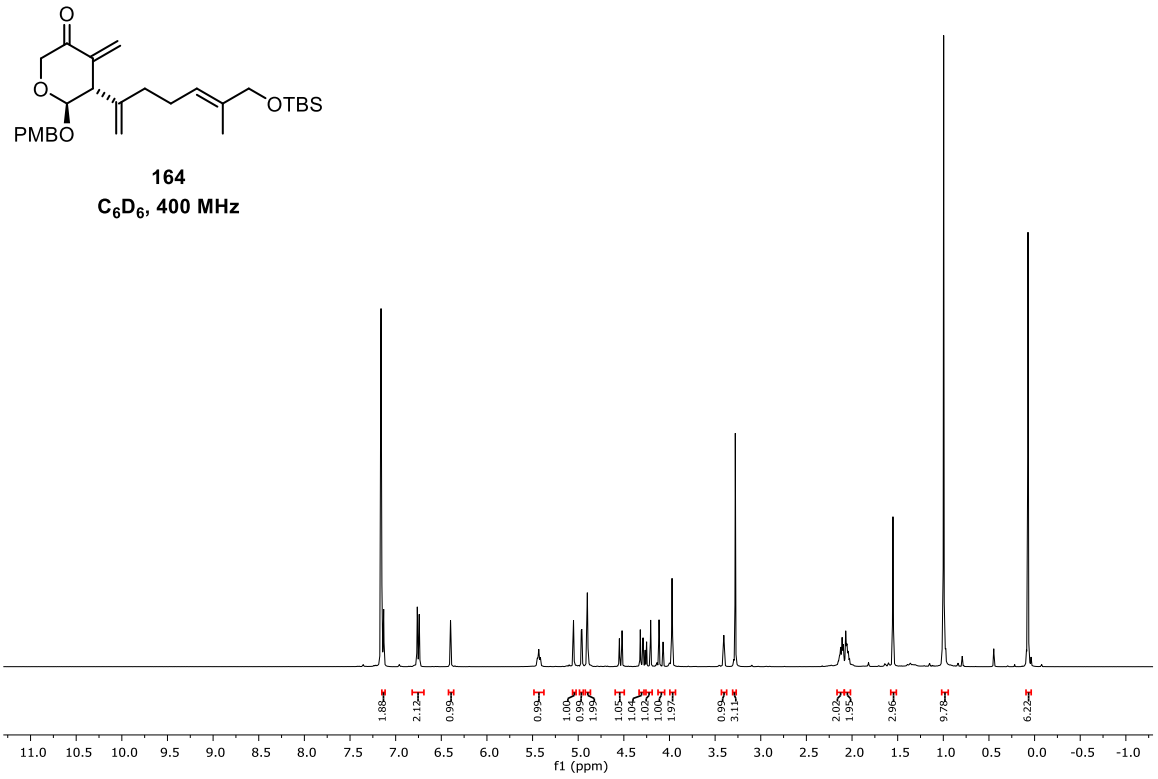
136
$CDCl_3$, 100 MHz



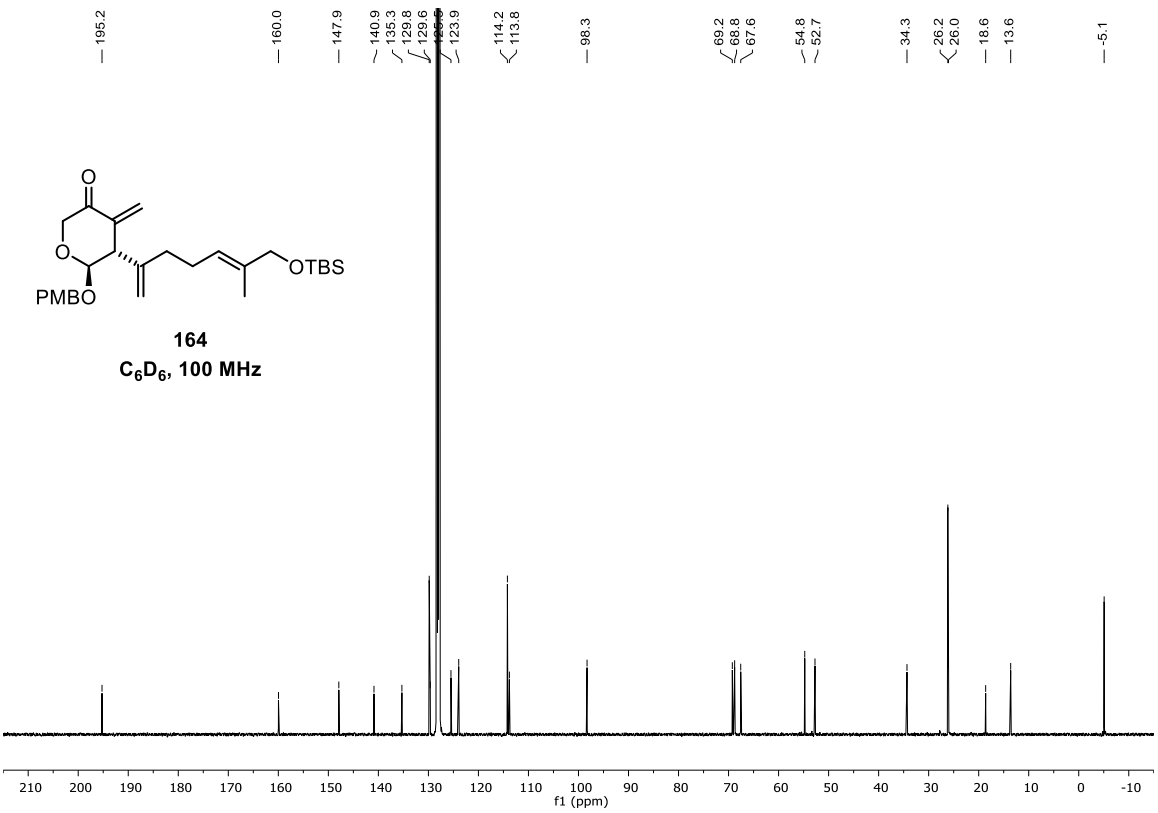
163
$CDCl_3$, 600 MHz



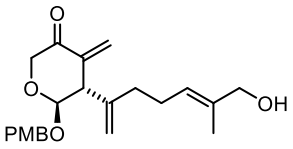
163
$CDCl_3$, 150 MHz



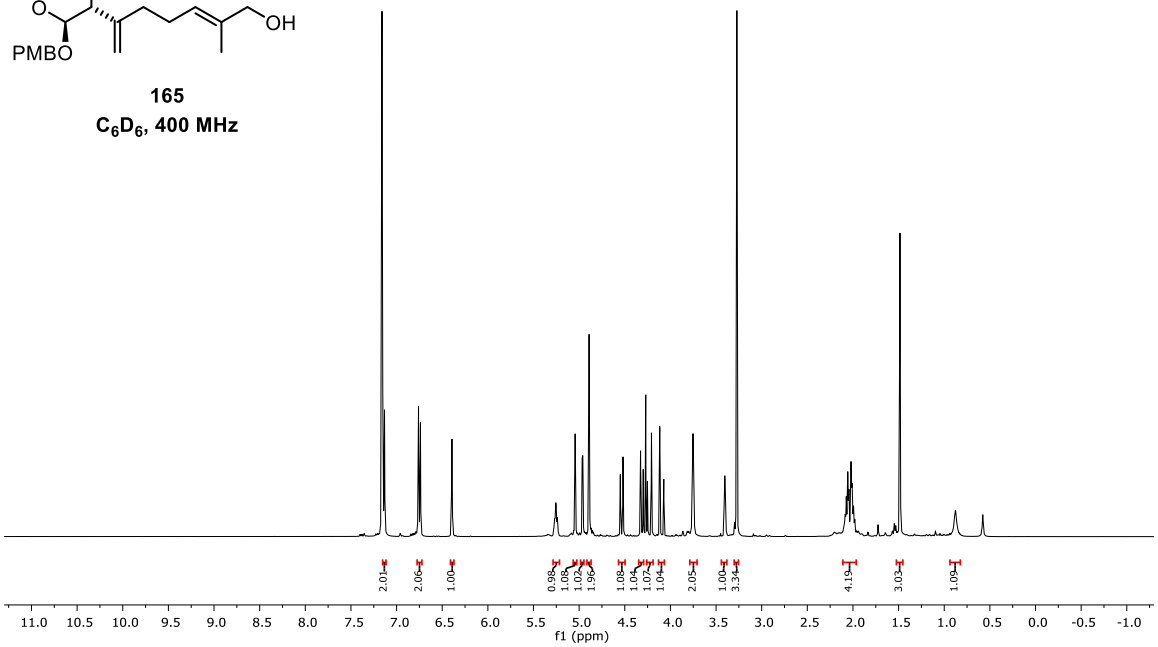
164
C_6D_6, 400 MHz

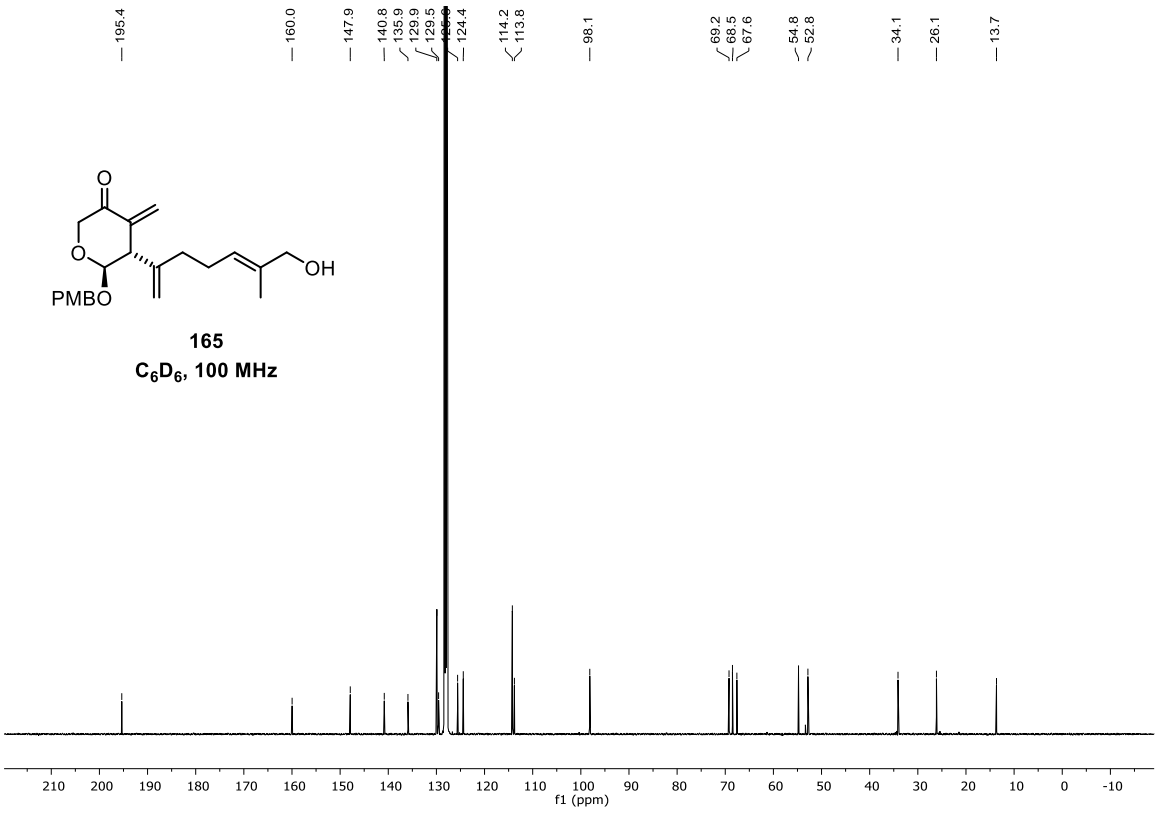


164
C_6D_6, 100 MHz

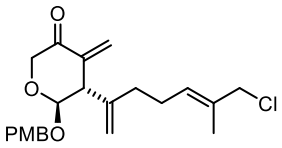


165
C_6D_6, 400 MHz

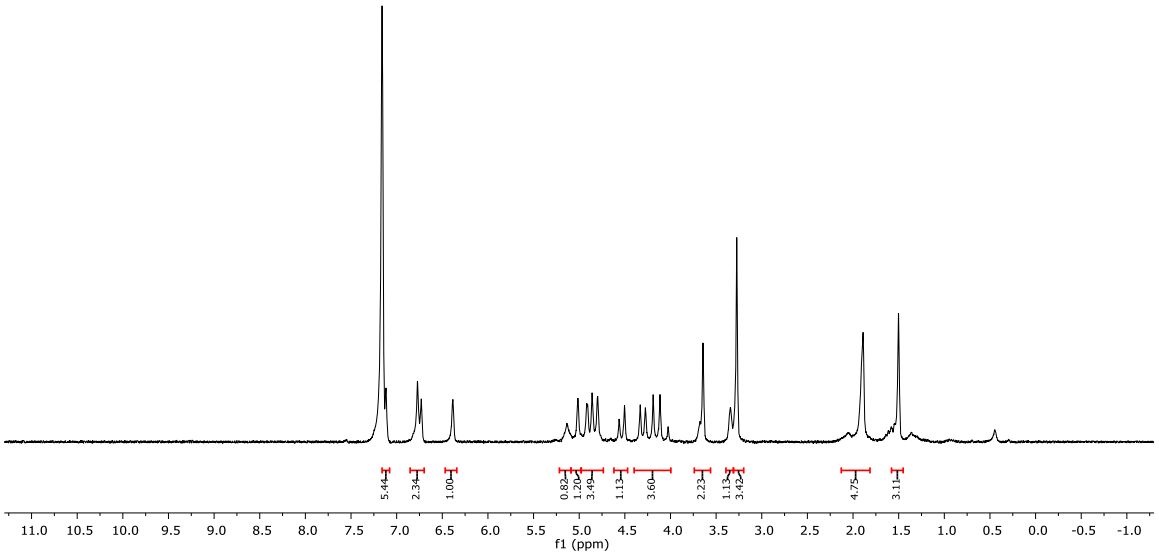


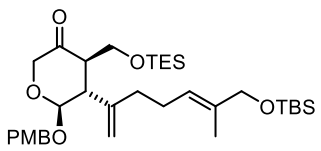


165
C_6D_6, 100 MHz

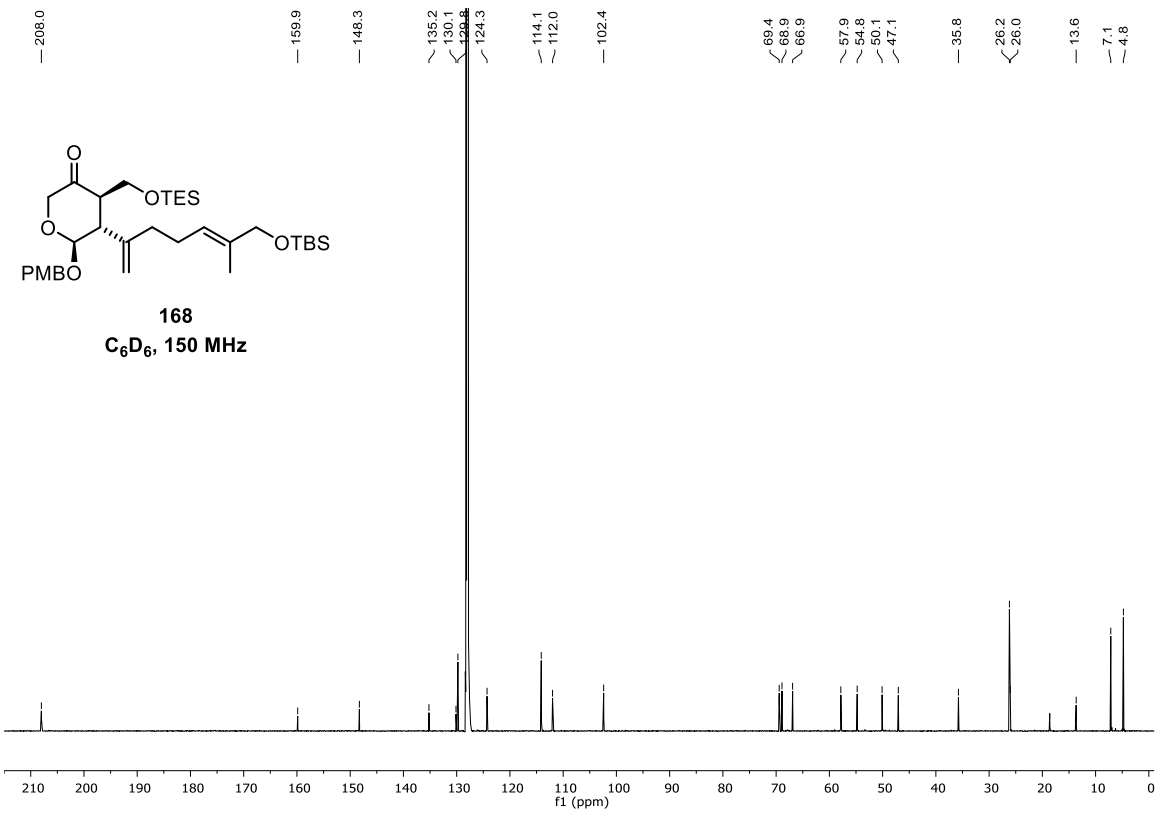


156
C_6D_6, 200 MHz

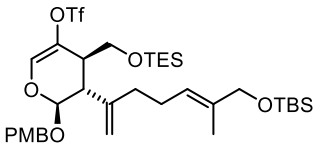




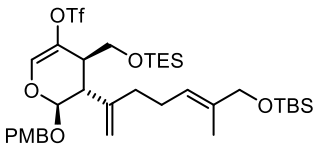
168
C_6D_6, 600 MHz



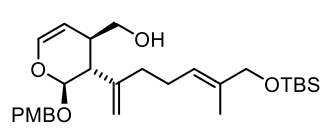
168
C_6D_6, 150 MHz



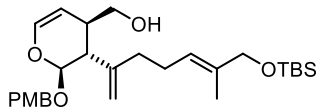
169
C_6D_6, 600 MHz



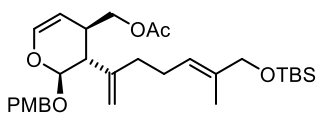
169
C_6D_6, 150 MHz



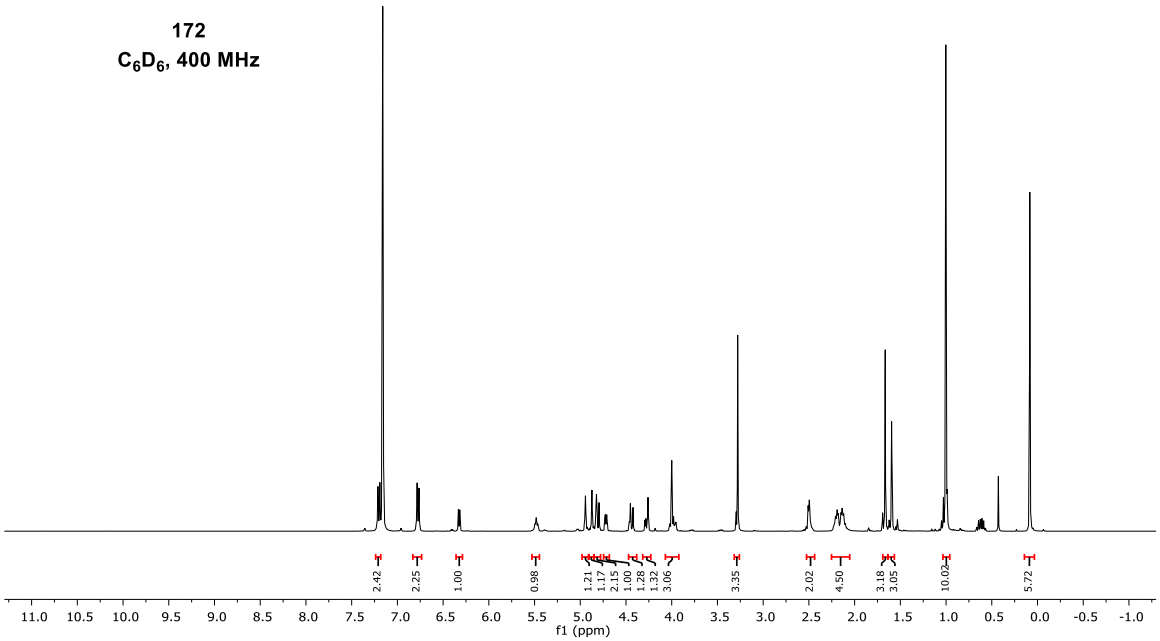
171
C_6D_6, 400 MHz

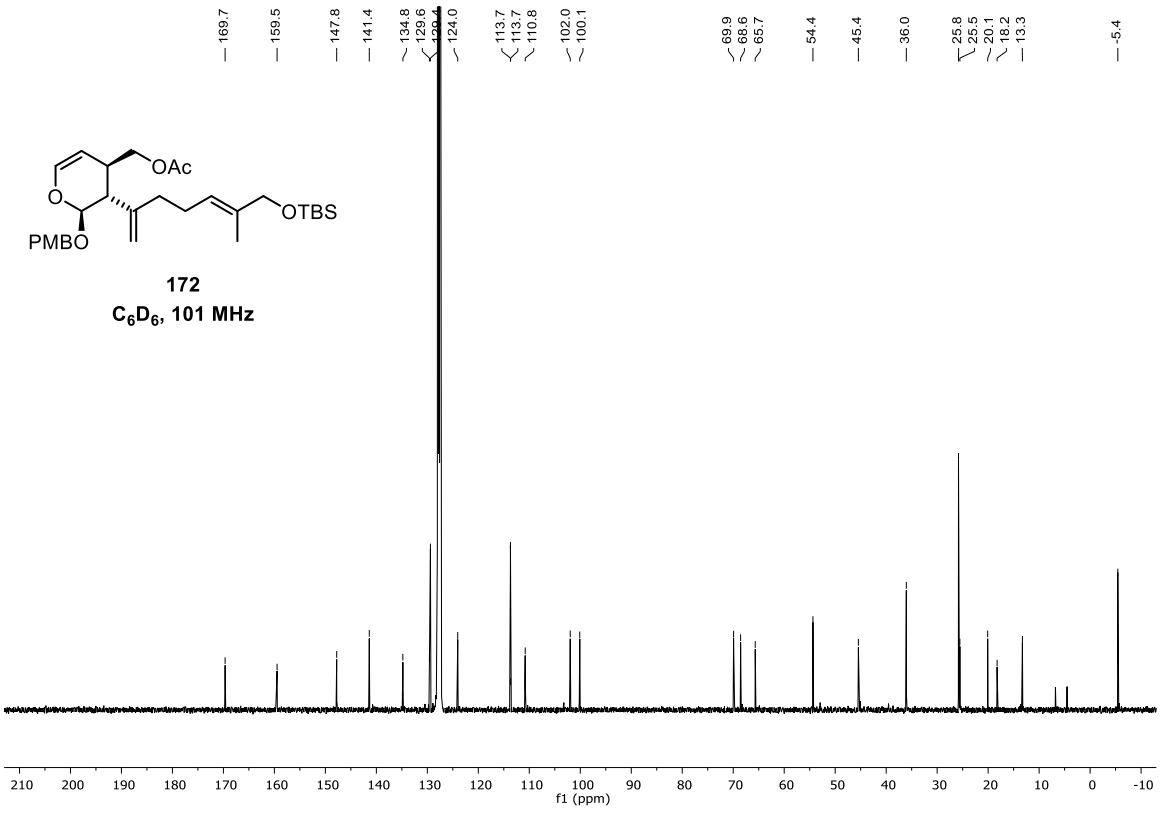


171
C_6D_6, 100 MHz

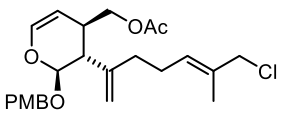


172
C_6D_6, 400 MHz

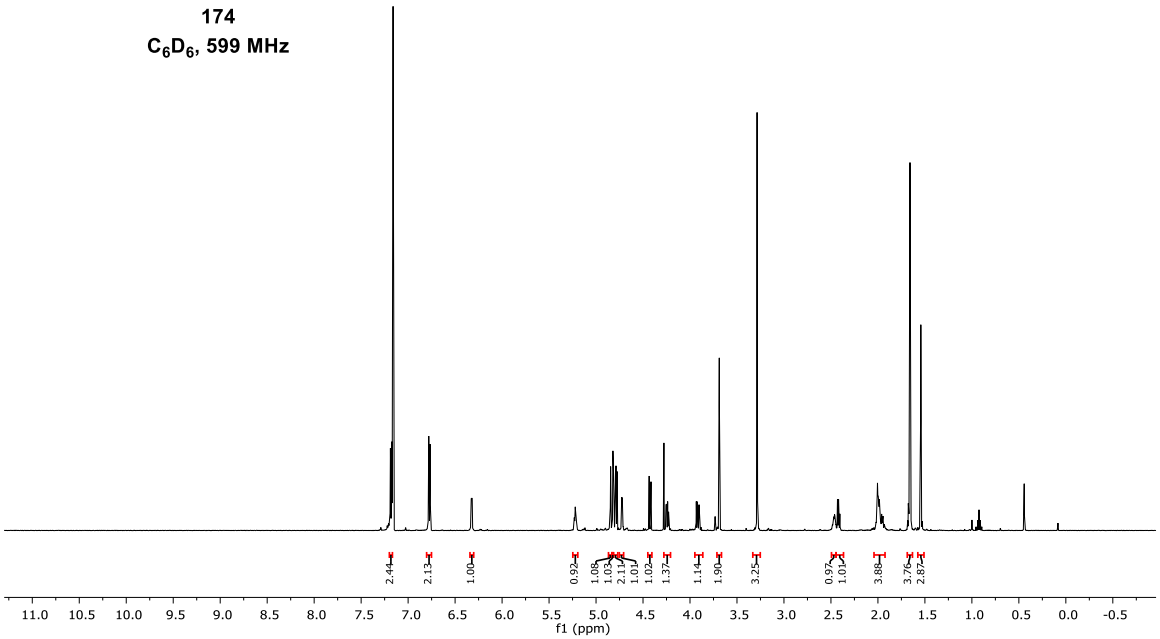


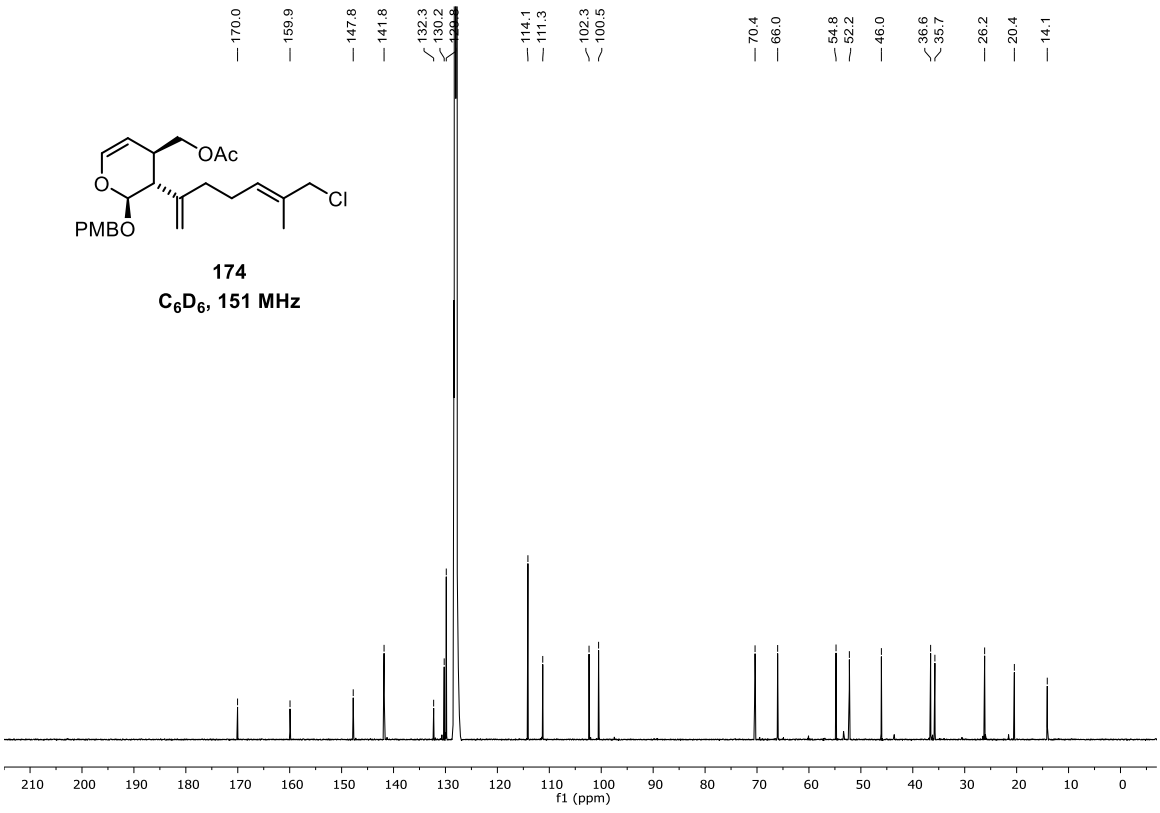


172
C_6D_6, 101 MHz

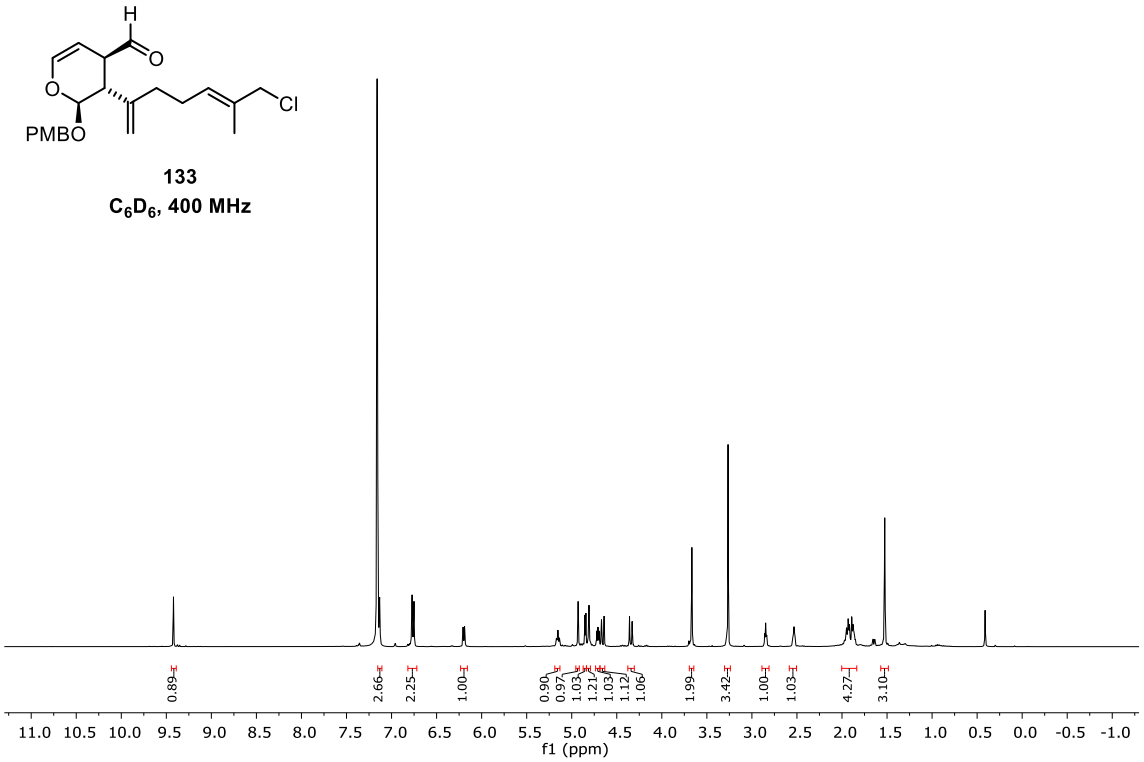


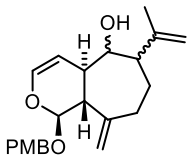
174
C_6D_6, 599 MHz



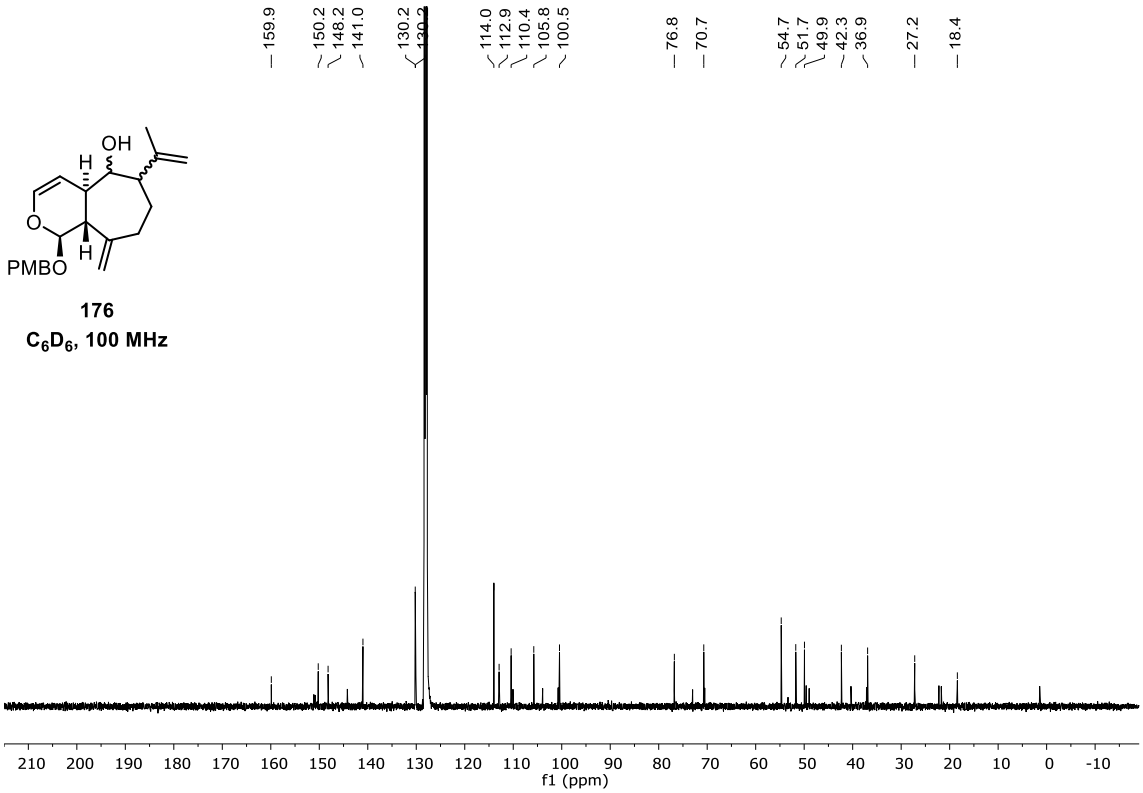


174
C_6D_6, 151 MHz

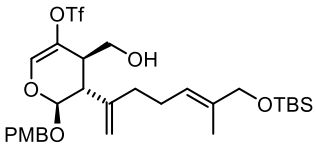

H
O
O
PMBO
Cl
133
C6D6, 400 MHz
0.89
2.66
2.25
1.00
0.90
0.97
1.03
1.21
1.03
1.12
1.06
1.99
3.42
1.00
1.03
4.27
3.10
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



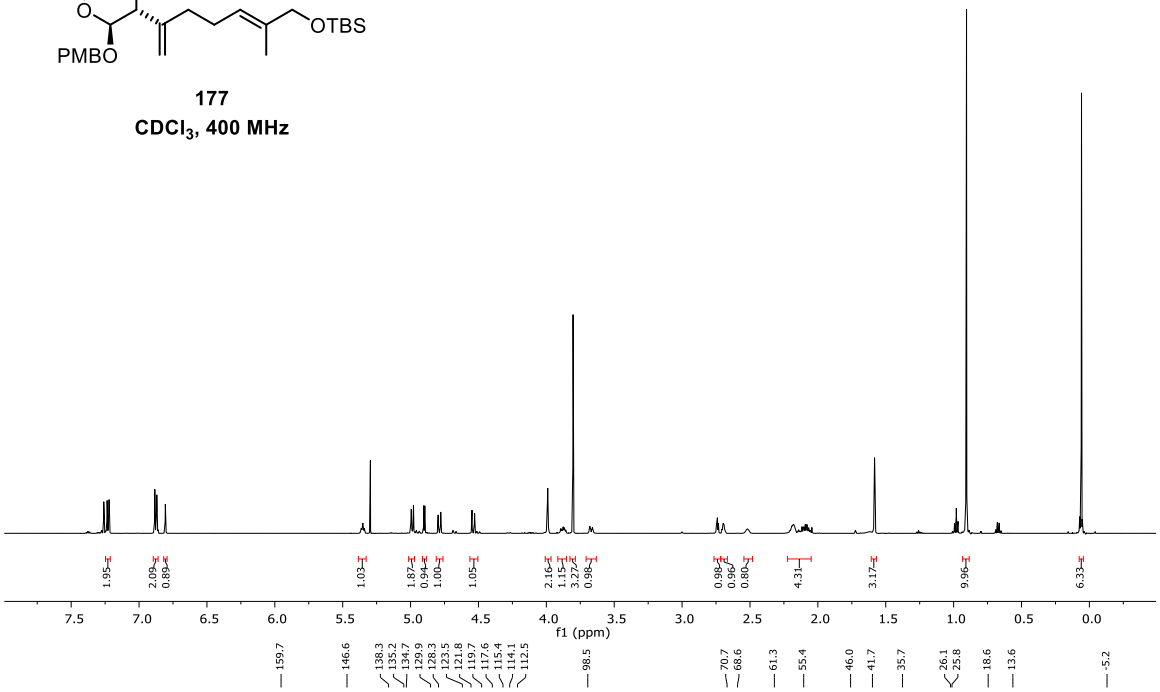
176
C_6D_6, 400 MHz

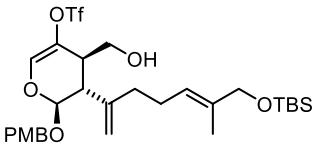


176
C_6D_6, 100 MHz

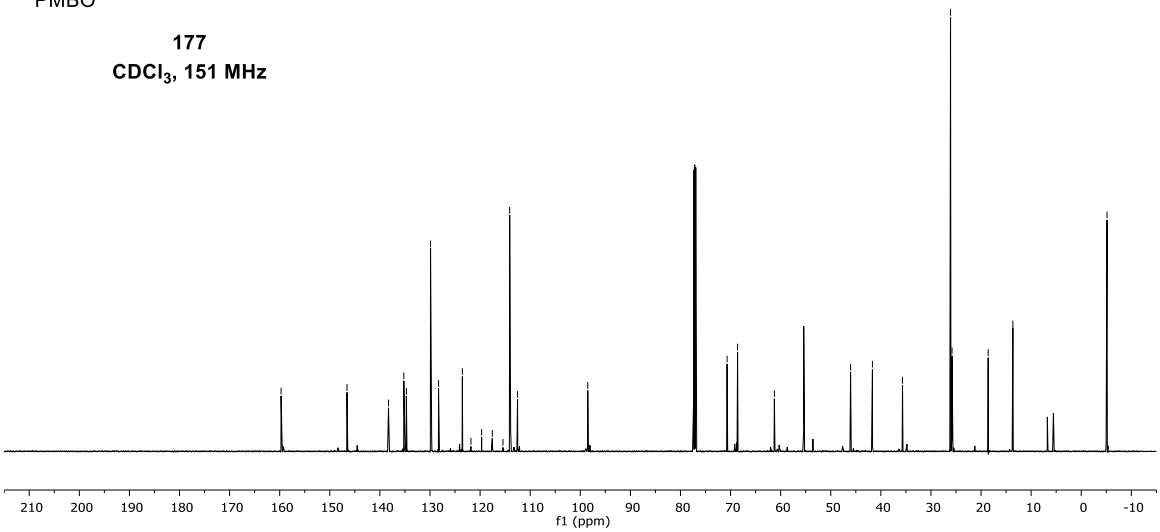


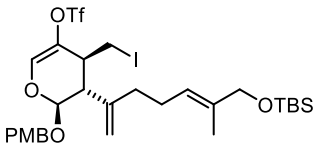
177
$CDCl_3$, 400 MHz



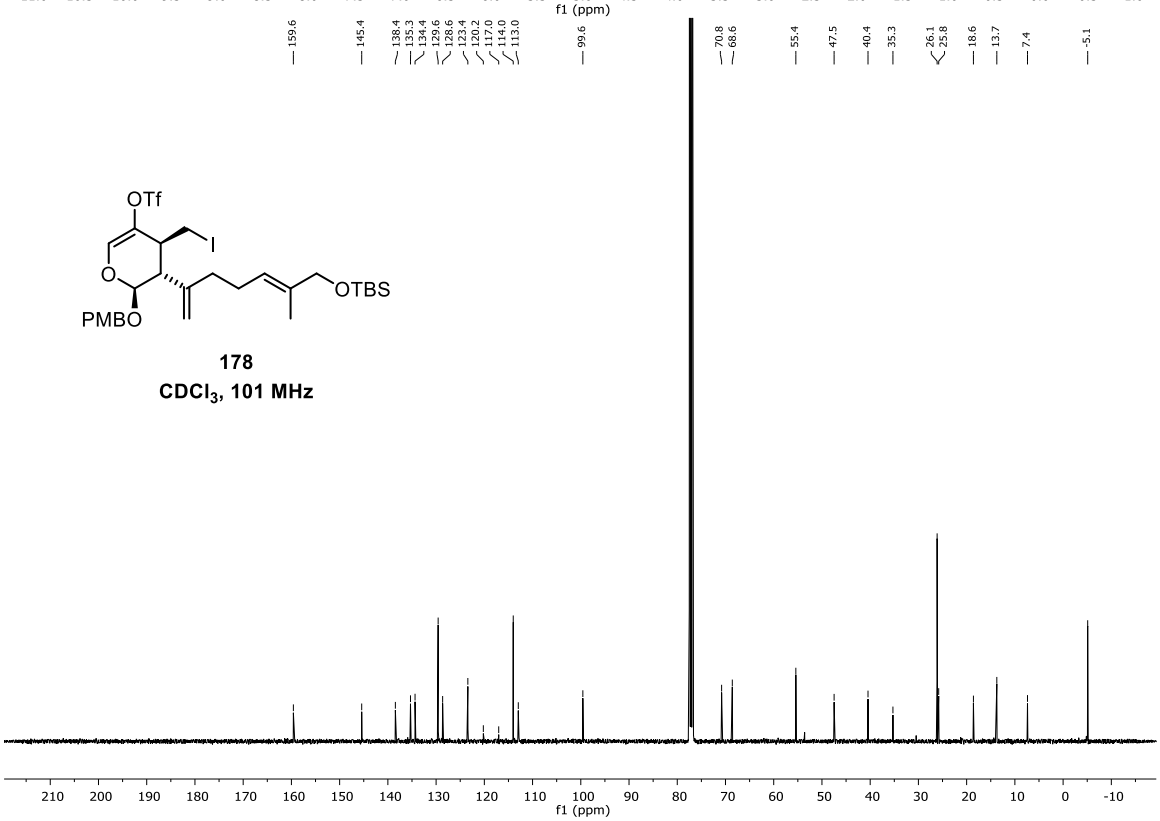


177
$CDCl_3$, 151 MHz

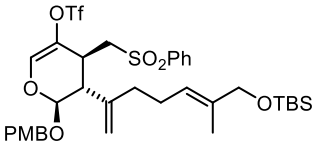




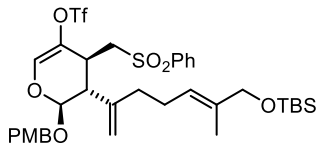
178
$CDCl_3$, 400 MHz



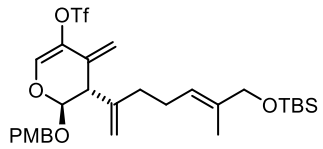
178
$CDCl_3$, 101 MHz



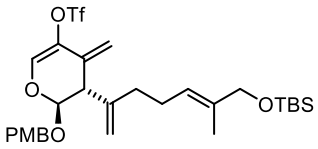
179
$CDCl_3$, 599 MHz



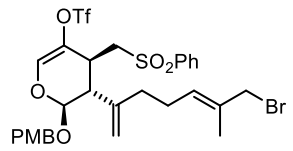
179
$CDCl_3$, 151 MHz



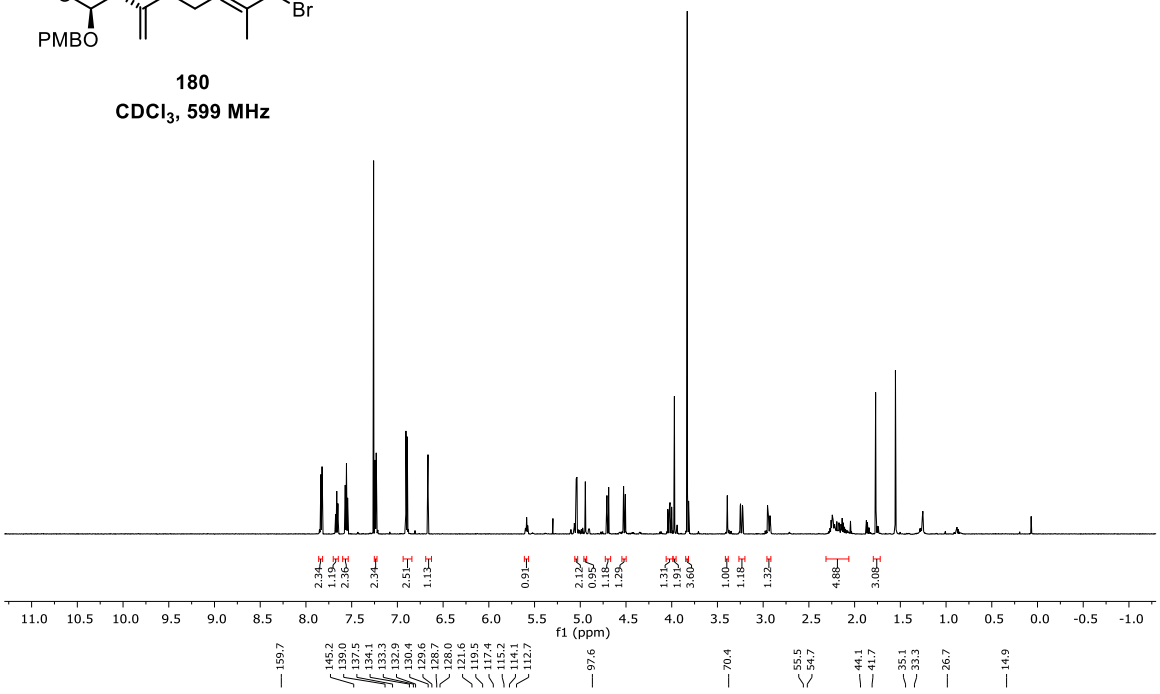
S3
$CDCl_3$, 599 MHz

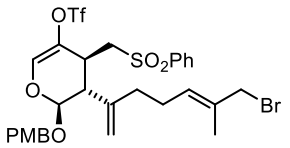


S3
$CDCl_3$, 151 MHz

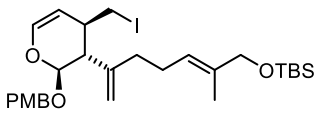


180
$CDCl_3$, 599 MHz

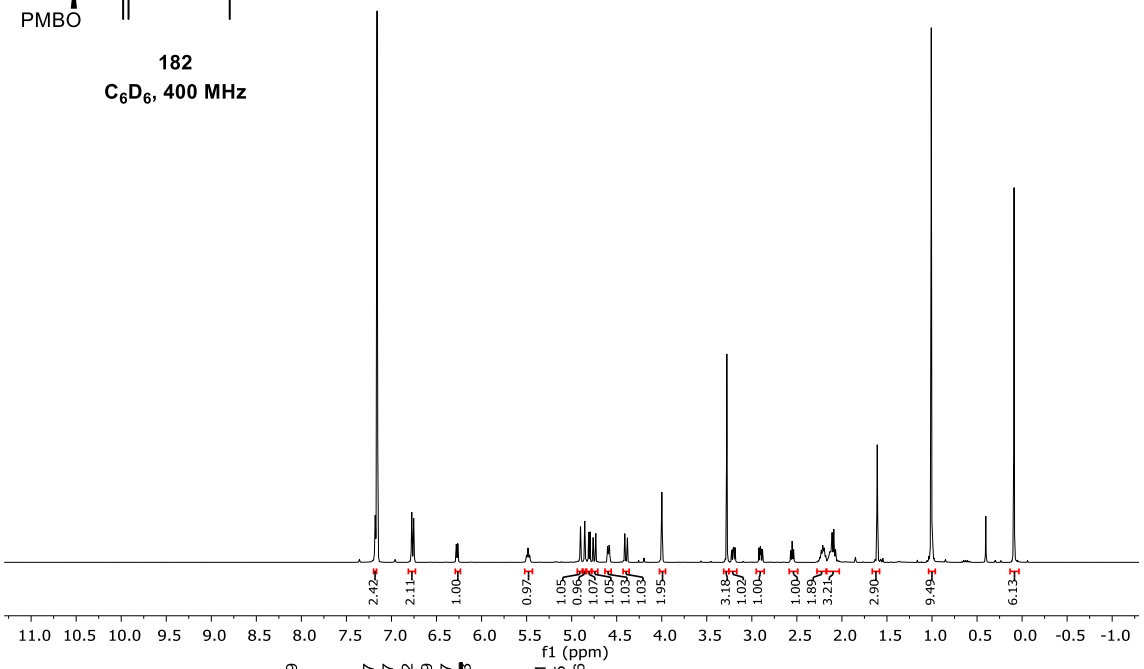


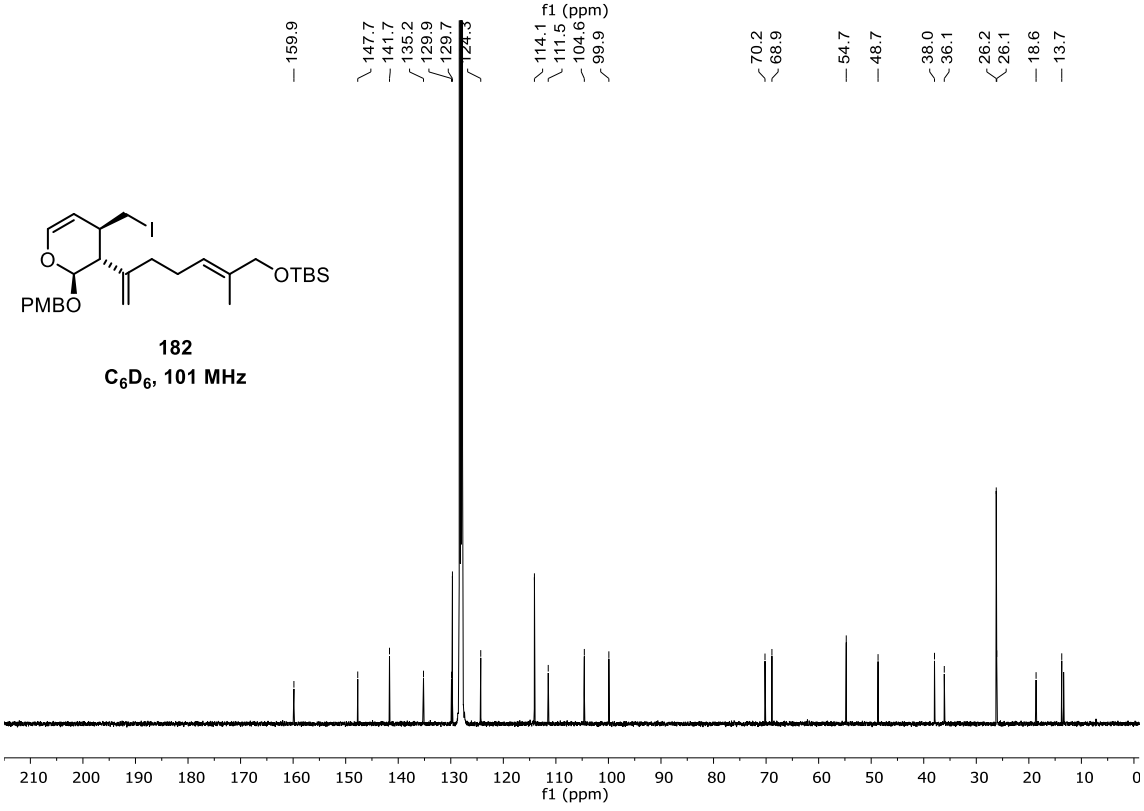


180
$CDCl_3$, 151 MHz

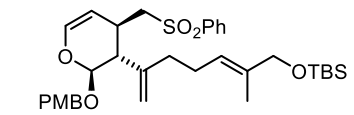


182
C_6D_6, 400 MHz

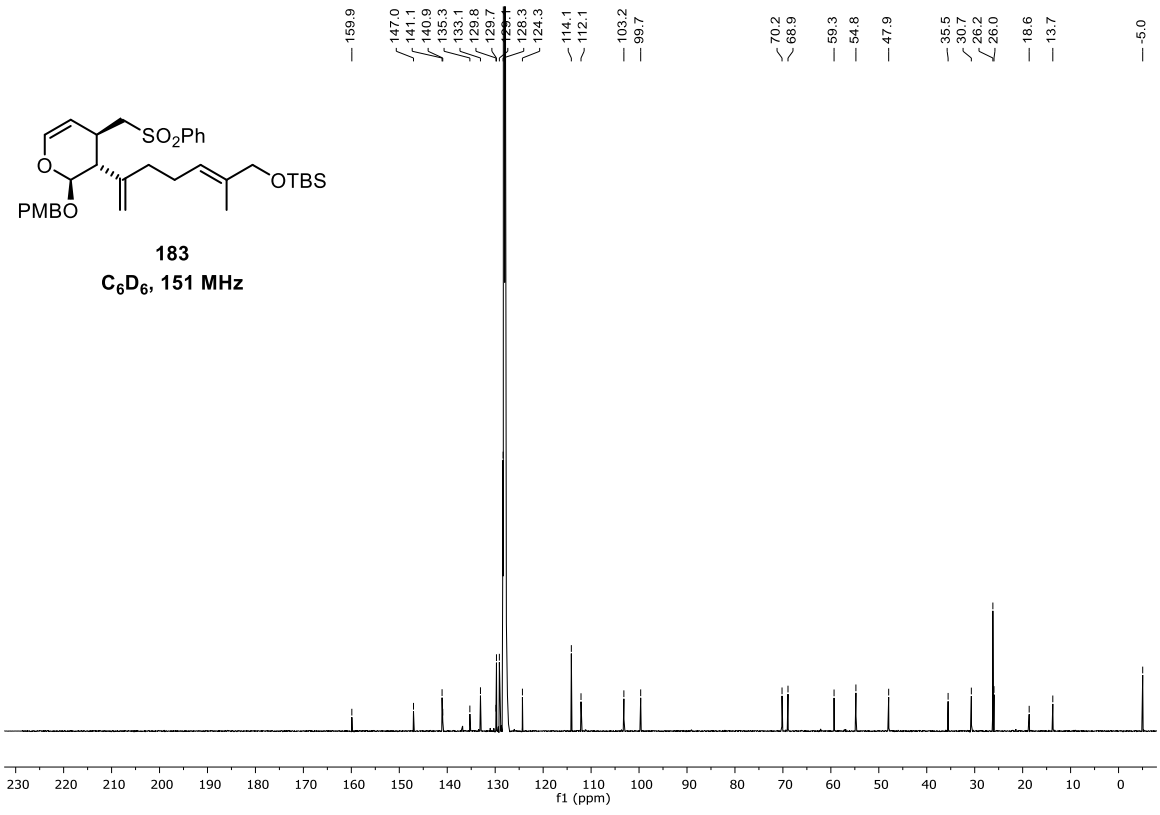




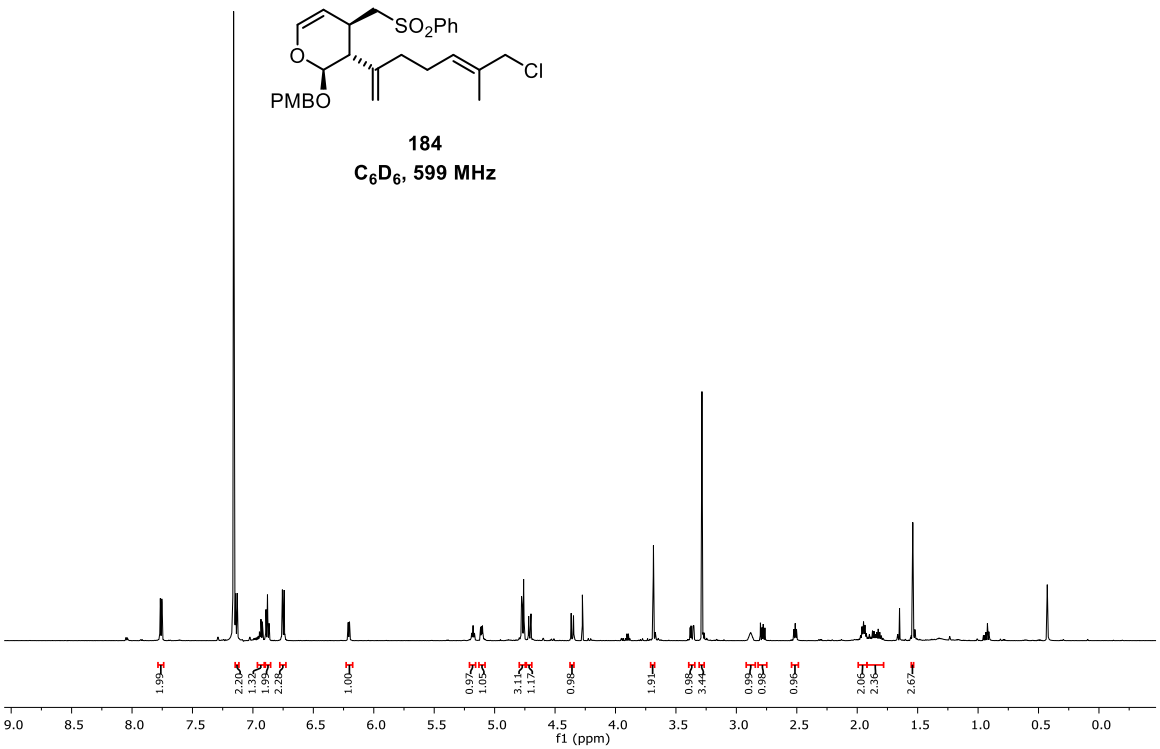
182
C_6D_6, 101 MHz



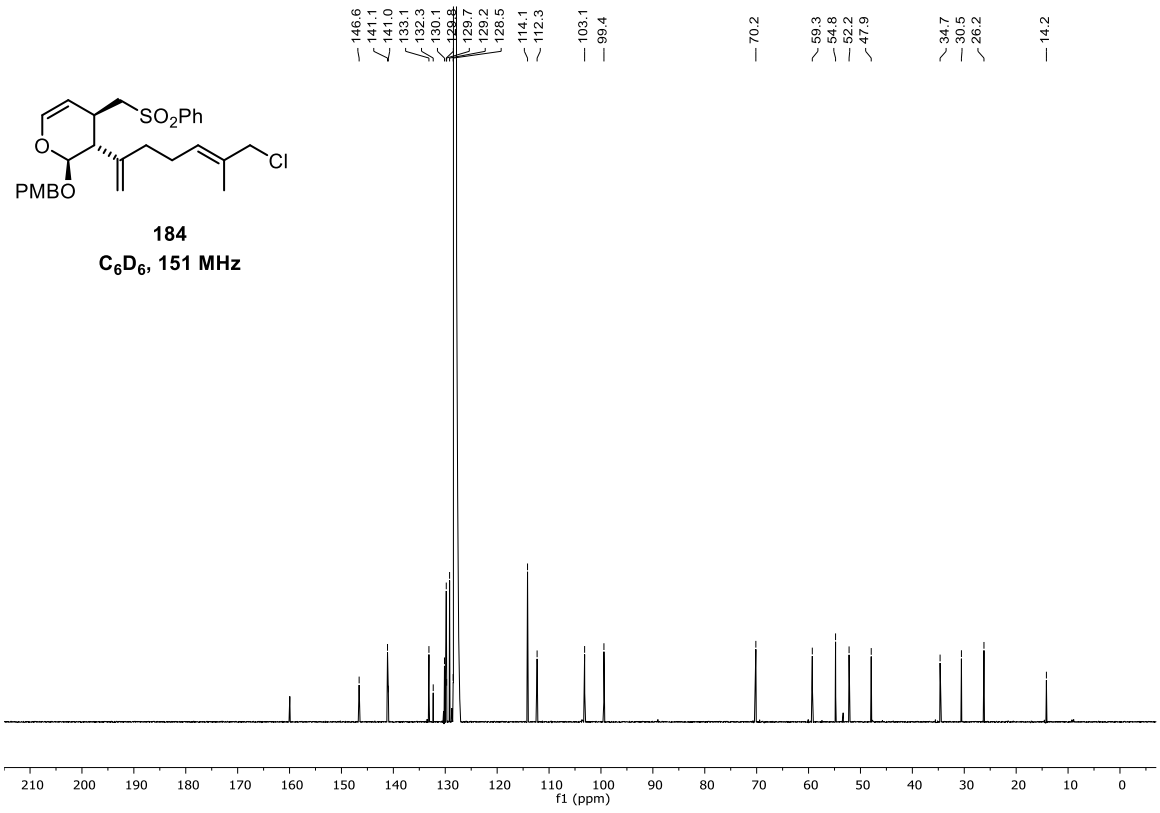
183
C_6D_6, 599 MHz



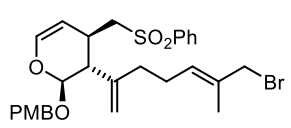
183
C_6D_6, 151 MHz



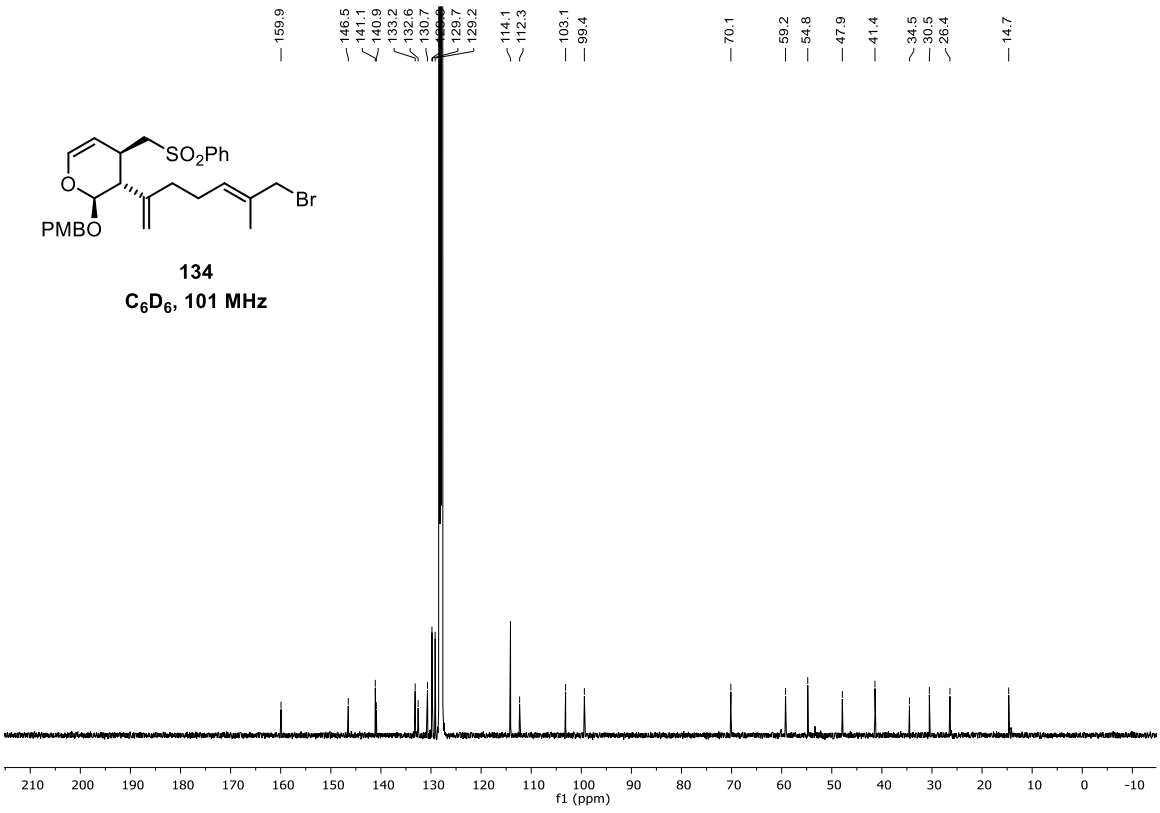
184
C_6D_6, 599 MHz



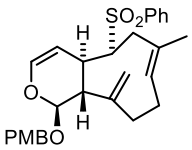
184
C_6D_6, 151 MHz



134
C_6D_6, 400 MHz

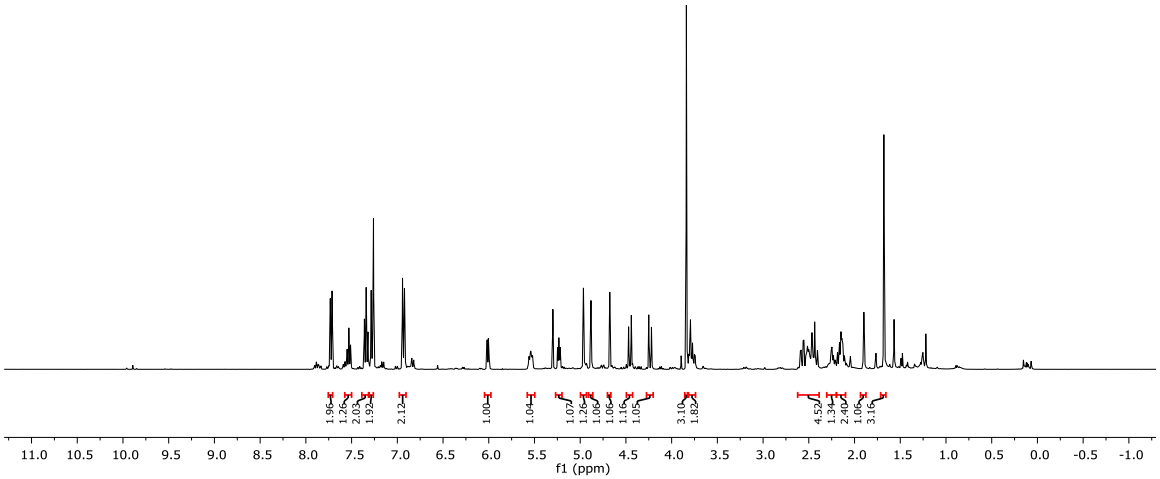


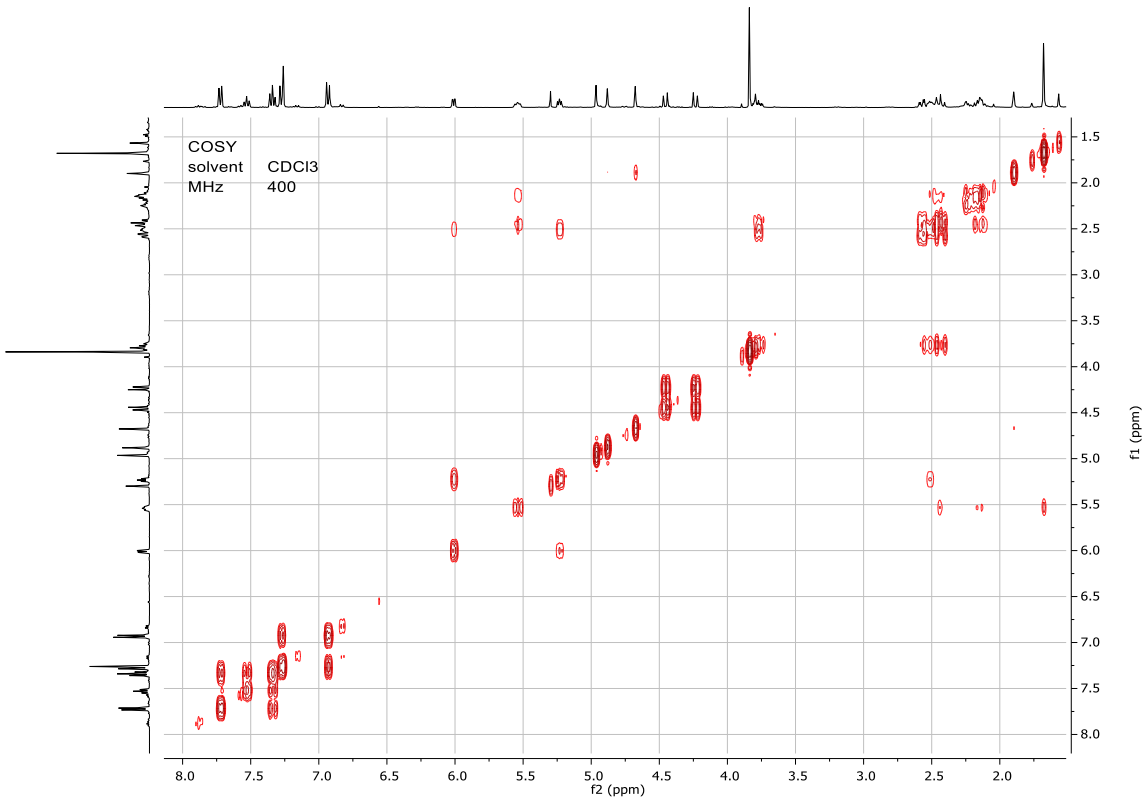
134
C_6D_6, 101 MHz

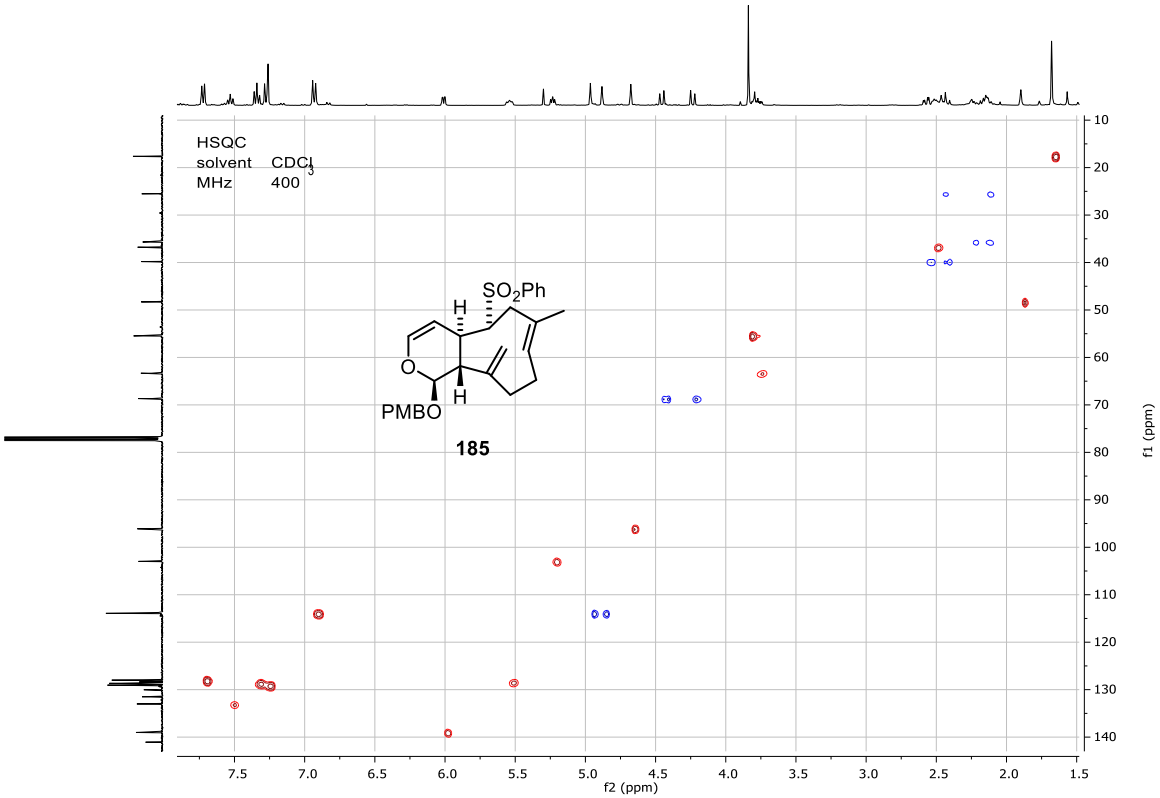


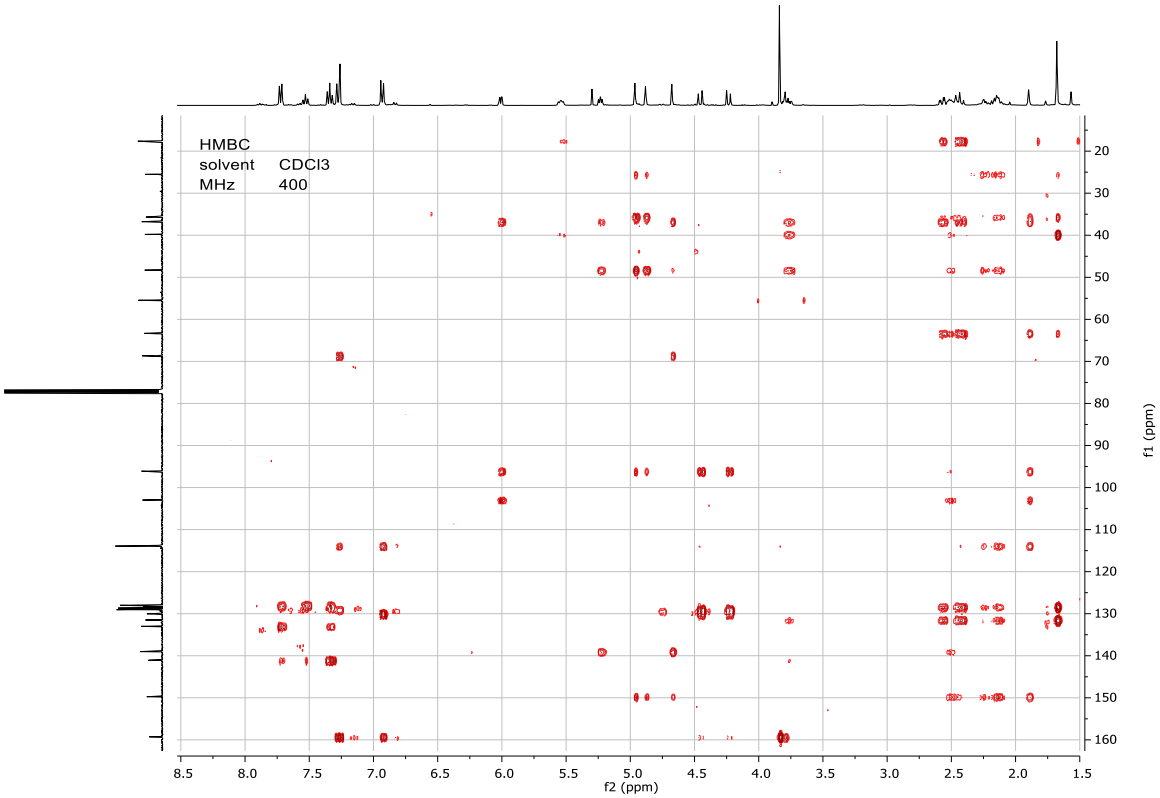
185

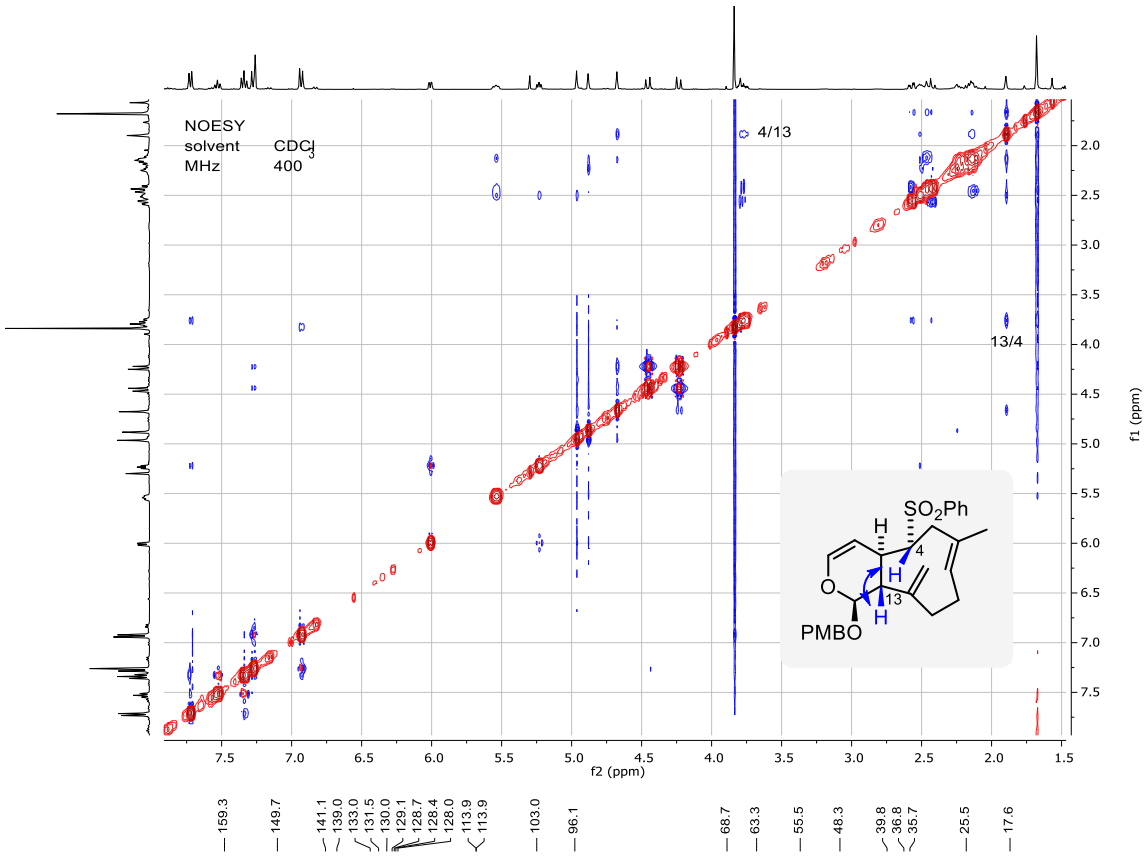
$CDCl_3$, 400 MHz

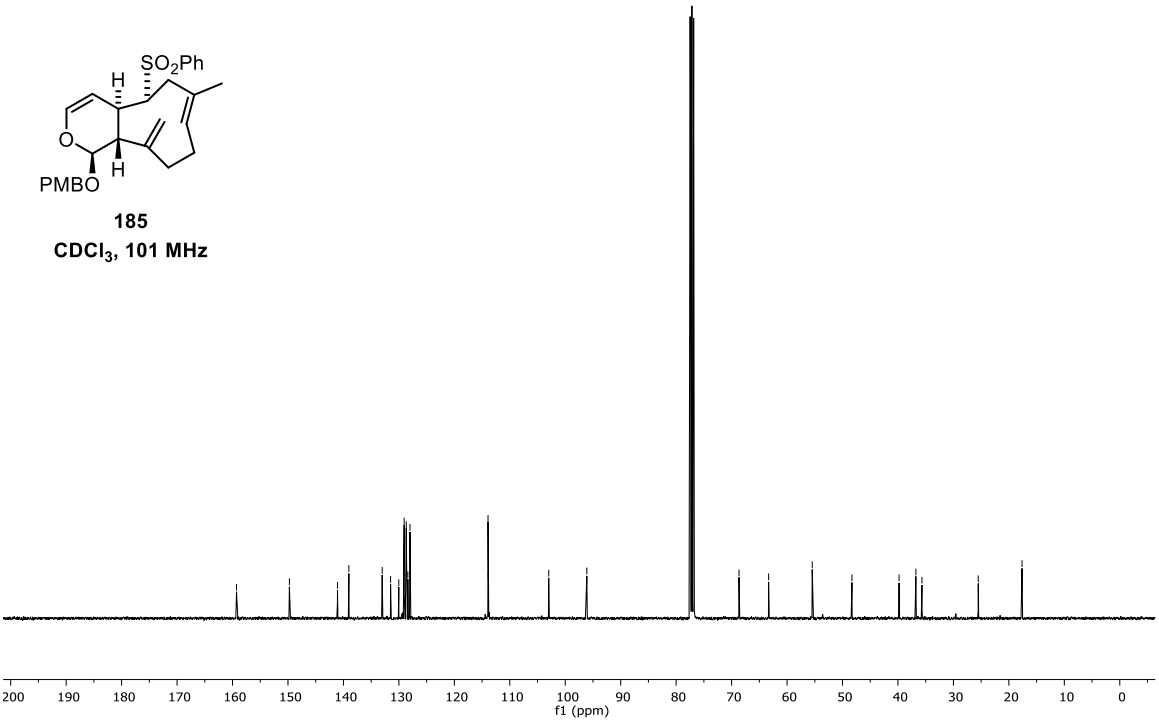




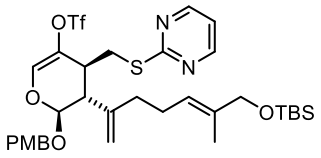

HSQC
solvent CDCl3
MHz 400
SO2Ph
H
O
H
PMBO
185
f2 (ppm)
f1 (ppm)


HMBC
solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

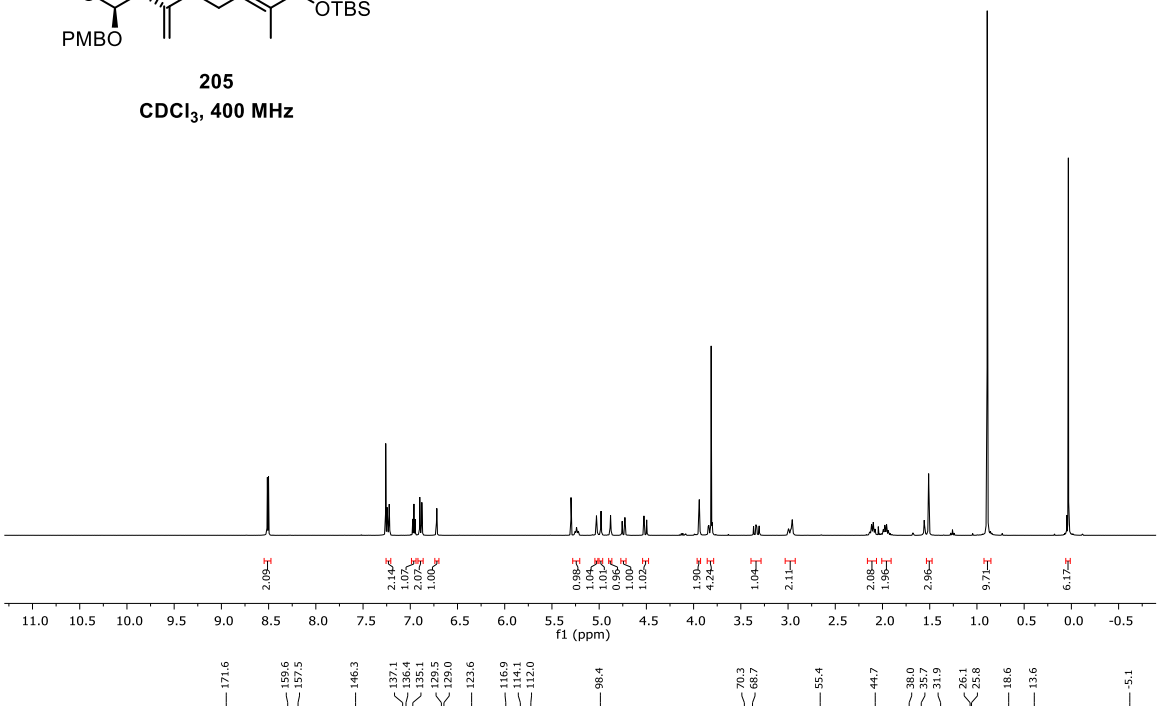


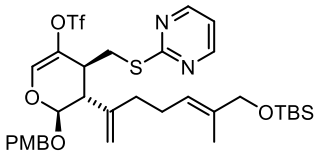


185
$CDCl_3$, 101 MHz

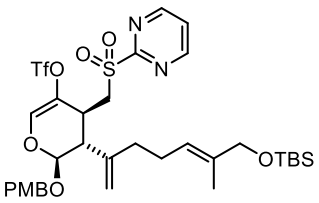


205
$CDCl_3$, 400 MHz

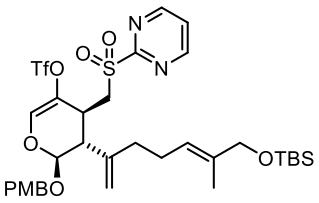




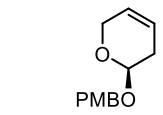
205
$CDCl_3$, 101 MHz



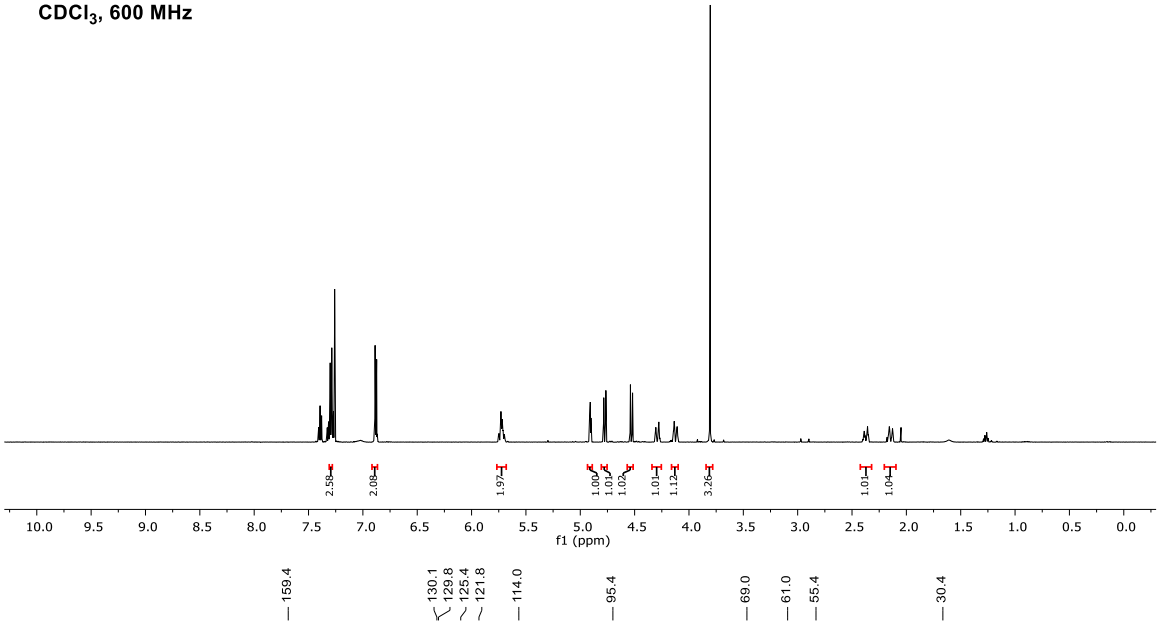
206
$CDCl_3$, 599 MHz

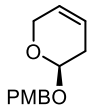


206
$CDCl_3$,151 MHz

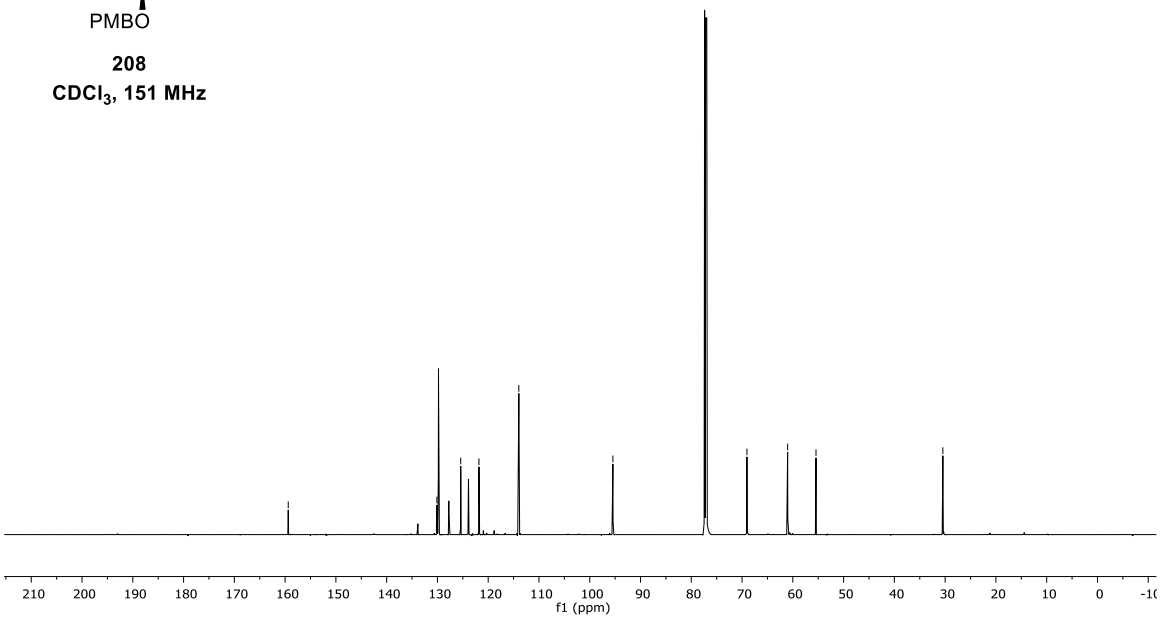


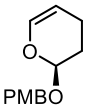
208
$CDCl_3$, 600 MHz



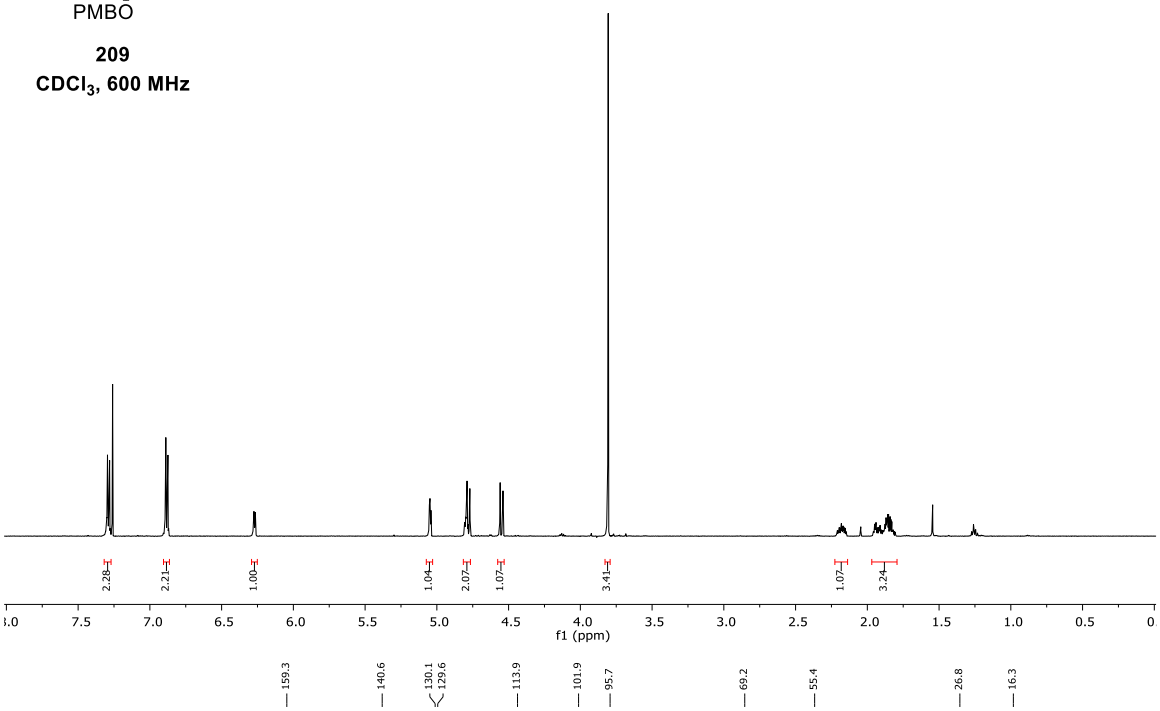


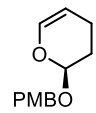
208
$CDCl_3$, 151 MHz



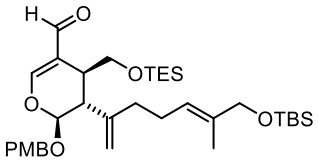


209
$CDCl_3$, 600 MHz

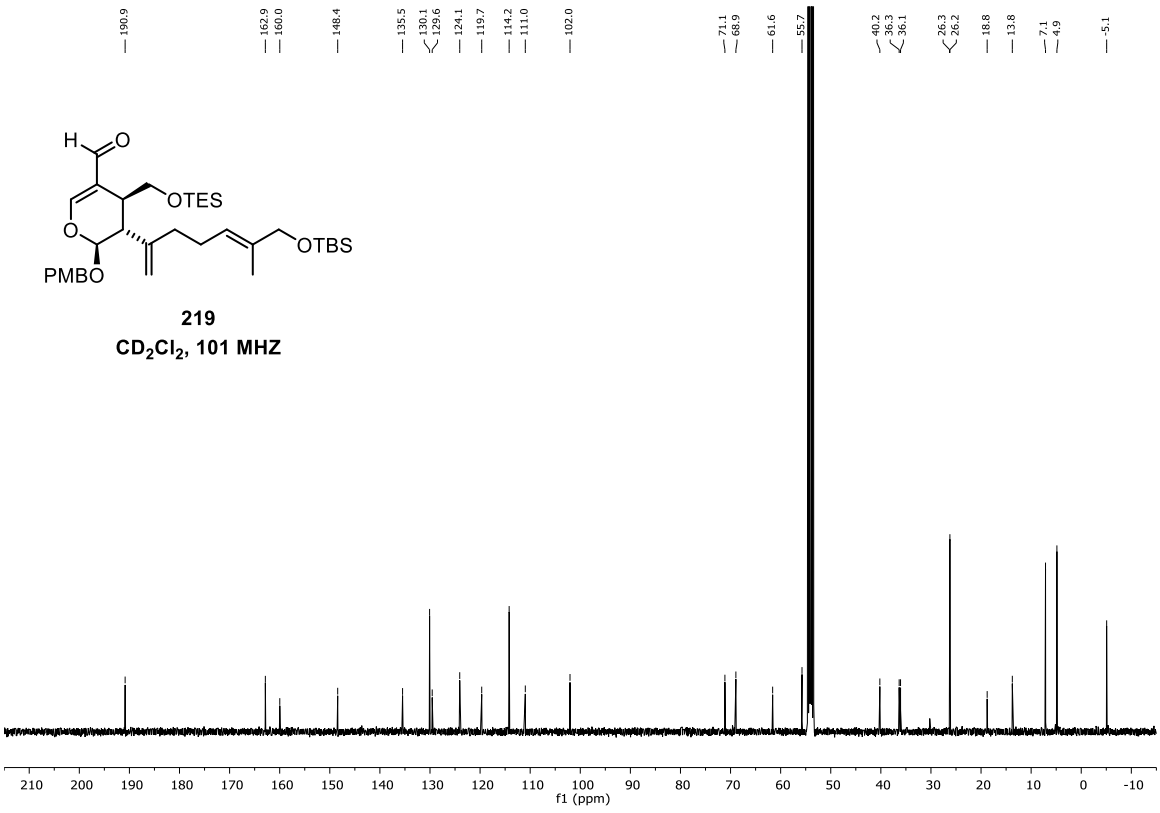




209
$CDCl_3$, 151 MHz



219
CD_2Cl_2, 400 MHZ



219
CD_2Cl_2, 101 MHZ

9.4 Single Crystal X-ray Analysis

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[163] and refined by least-squares methods against *F*2 with SHELXL-97.[164] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

Lactol 76.

Table 22. Crystallographic data for lactol **76**.

net formula	$C_{22}H_{40}O_5Si_2$
***M*$_r$/g mol^{-1}**	440.72
crystal size/mm	0.100 × 0.080 × 0.070
***T*/K**	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	'P -1'
***a*/Å**	7.1851(4)
***b*/Å**	13.9847(7)
***c*/Å**	25.4831(14)
α/°	92.4216(16)
β/°	89.9812(18)
γ/°	105.0653(17)
***V*/Å^3**	2470.2(2)
Z	4
calc. density/g cm^{-3}	1.185
μ/mm^{-1}	0.172
absorption correction	multi-scan
transmission factor range	0.8209–0.9582
refls. measured	25444
***R*$_{int}$**	0.0444
mean σ(*I*)/*I*	0.0539
θ range	2.400–25.41
observed refls.	7262
***x, y* (weighting scheme)**	0.0632, 1.2490
hydrogen refinement	mixed

refls in refinement	9097
parameters	542
restraints	1
***R*(*F*$_{obs}$)**	0.0482
***R*$_w$(*F*^{2})**	0.1275
S	1.029
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.564
min electron density/e Å^{-3}	−0.377

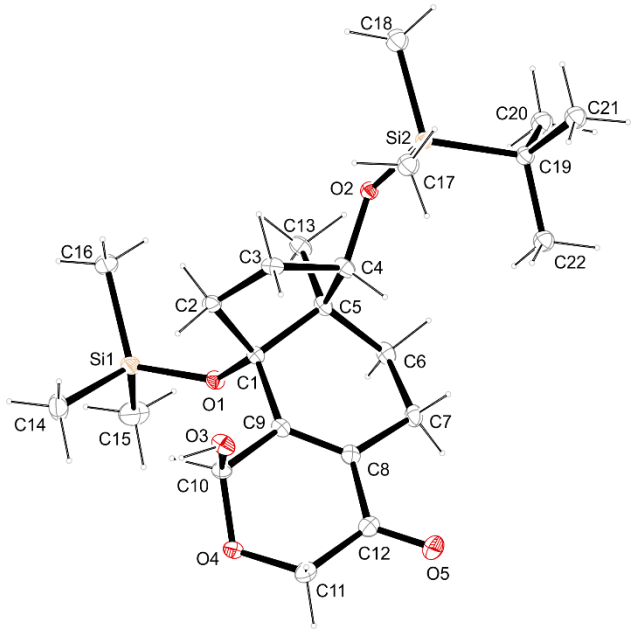


Figure 12. Molecular structure of lactol **76**. Ellipsoids are drawn at 50% probability level.

Aldehyde 111.

Table 23. Crystallographic data for aldehyde **111**.

net formula	$C_{32}H_{50}O_8Si$
***M*$_r$/g mol^{-1}**	590.81
crystal size/mm	0.100 × 0.080 × 0.040
***T*/K**	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
***a*/Å**	8.2999(2)

***b*/Å**	9.1317(2)
***c*/Å**	21.9845(5)
α/°	79.5184(7)
β/°	86.2304(7)
γ/°	77.7532(7)
***V*/Å^3**	1600.52(6)
Z	2
calc. density/g cm^{-3}	1.226
μ/mm^{-1}	0.121
absorption correction	Multi-Scan
transmission factor range	0.9066–0.9420
refls. measured	41425
R_{int}	0.0259
mean σ(*I*)/*I*	0.0235
θ range	3.184–30.508
observed refls.	8581
***x, y* (weighting scheme)**	0.0443, 0.6035
hydrogen refinement	constr
refls in refinement	9740
parameters	379
restraints	1
$R(F_{obs})$	0.0344
$R_w(F^2)$	0.0959
S	1.040
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.445
min electron density/e Å^{-3}	−0.266

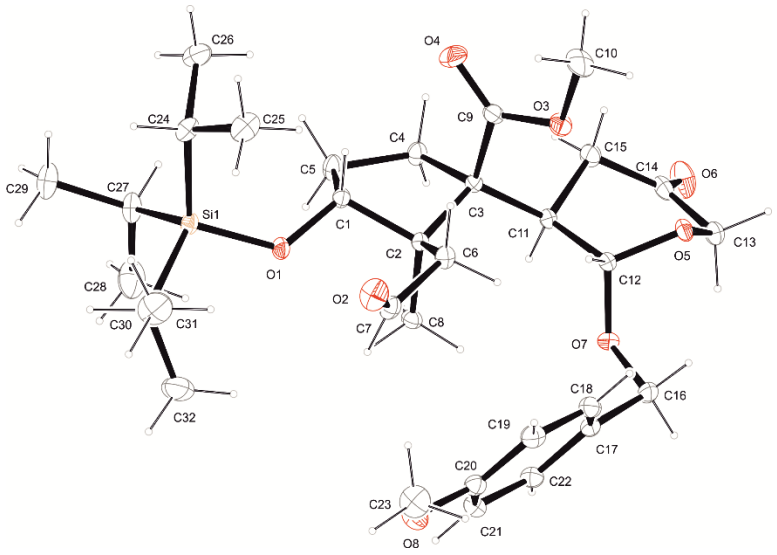


Figure 13. Molecular structure of aldehyde **111**. Ellipsoids are drawn at 50% probability level.

Enone 112.

Table 24. Crystallographic data for enone **112**.

net formula	$C_{32}H_{48}O_7Si$
M_r/g mol^{-1}	572.79
crystal size/mm	0.080 × 0.050 × 0.030
***T*/K**	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
***a*/Å**	8.4856(6)
***b*/Å**	13.1092(10)
***c*/Å**	27.727(2)
α/°	90.520(3)
β/°	90.331(3)
γ/°	91.105(3)
***V*/Å^3**	3083.6(4)
Z	4
calc. density/g cm^{-3}	1.234
μ/mm^{-1}	0.121
absorption correction	Multi-Scan
transmission factor range	0.8637–0.9705

refls. measured	42452
R_{int}	0.0555
mean σ(*I*)/*I*	0.0704
θ range	3.188–28.282
observed refls.	12184
***x*, *y* (weighting scheme)**	0.0506, 10.3791
hydrogen refinement	constr
refls in refinement	15254
parameters	740
restraints	0
$R(F_{obs})$	0.0806
$R_w(F^2)$	0.2024
S	1.079
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	1.114
min electron density/e Å^{-3}	−0.636

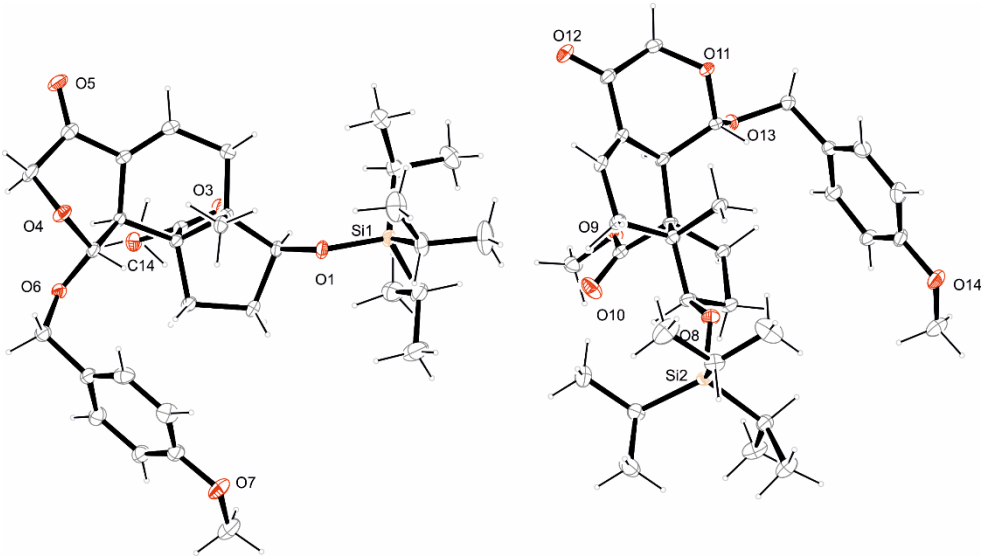


Figure 14. Molecular structure of enone **112**. Ellipsoids are drawn at 50% probability level.

Tetracycle 116.

Table 25. Crystallographic data for tetracycle **116**.

net formula	$C_{22}H_{26}O_6$
M_r/g mol^{-1}	386.43
crystal size/mm	0.090 × 0.070 × 0.060
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	17.8424(7)
b/Å	12.7737(5)
c/Å	8.4584(3)
α/°	90
β/°	100.3920(10)
γ/°	90
V/Å^3	1896.16(12)
Z	4
calc. density/g cm^{-3}	1.354
μ/mm^{-1}	0.098
absorption correction	Multi-Scan
transmission factor range	0.9080–0.9705
refls. measured	24636
R_{int}	0.0360
mean σ(*I*)/*I*	0.0231
θ range	3.190–26.372
observed refls.	3354
***x, y* (weighting scheme)**	0.0321, 1.4007
hydrogen refinement	constr
refls in refinement	3868
parameters	255
restraints	0
$R(F_{obs})$	0.0377
$R_w(F^2)$	0.0945
S	1.055
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.286
min electron density/e Å^{-3}	−0.253

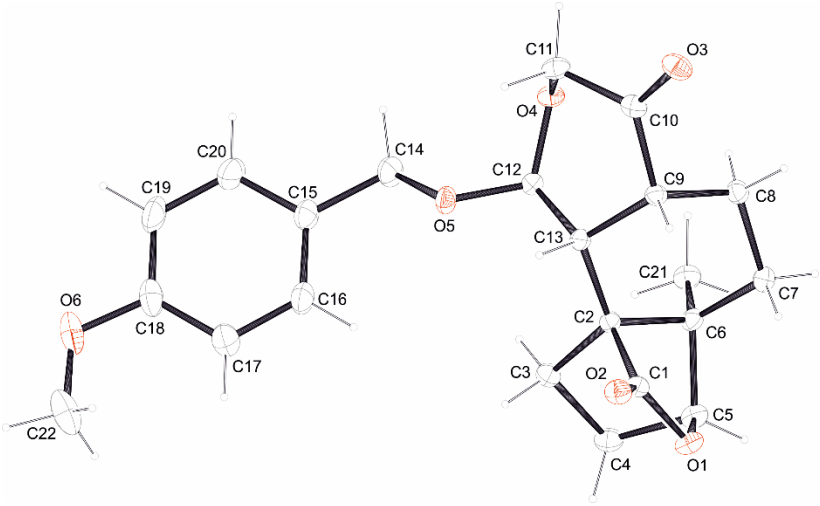


Figure 15. Molecular structure of tetracycle **116**. Ellipsoids are drawn at 50% probability level.

10. Experimental Section for Part II

Supporting Information

Development of a *β*-C–H Bromination Approach Toward the Synthesis of Jerantinine E

Tatjana Huber,[1,†] Teresa A. Preuhs,[1,†] Christa K. G. Gerlinger,[2] and Thomas Magauer*[,1,3]

[1]Department of Chemistry, Ludwig-Maximilians-University, 81377 Munich, Germany. [2]Faculty of Chemistry, University of Konstanz, 78457 Konstanz, Germany. [3]Institute of Organic Chemistry and Center for Molecular Biosciences, University of Innsbruck, 6020 Innsbruck, Austria.

The numbering of molecules in this chapter refers to the numbers in the article "*Development of a β-C–H Bromination Approach toward the Synthesis of Jerantinine E*" – T. Huber,[†] T. A. Preuhs,[†] C. K. G. Gerlinger, T. Magauer, *J. Org. Chem*. **2017**, *82*, 7410−7419; reprinted in chapter 7.4.

I. X-Ray Crystallographic Data

CCDC 1547827 contains the supplementary crystallographic data for tetrahydrocarbazolone **33**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

Table S1. Crystallographic data for tetrahydrocarbazolone **33**.

net formula	$C_{29}H_{29}NO_5$
M_r/g mol^{-1}	471.53
crystal size/mm	0.100×0.050×0.030
T/K	100(2)
radiation	Mo Kα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	10.5106(2)
b/Å	4.96800(10)
c/Å	44.4015(9)
α/°	90
β/°	91.3250(10)
γ/°	90
V/Å^3	2317.88(8)
Z	4
calc. density/g cm^{-3}	1.351
μ/mm^{-1}	0.092
absorption correction	Multi-Scan
transmission factor range	0.9211–0.9705

refls. measured	22871
R_{int}	0.0297
mean σ(*I*)/*I*	0.0256
θ range	3.331–26.372
observed refls.	4074
x, y (weighting scheme)	0.0343, 1.5990
hydrogen refinement	constr
refls in refinement	4723
parameters	319
restraints	0
$R(F_{obs})$	0.0395
$R_w(F^2)$	0.0946
S	1.038
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.263
min electron density/e Å^{-3}	−0.209

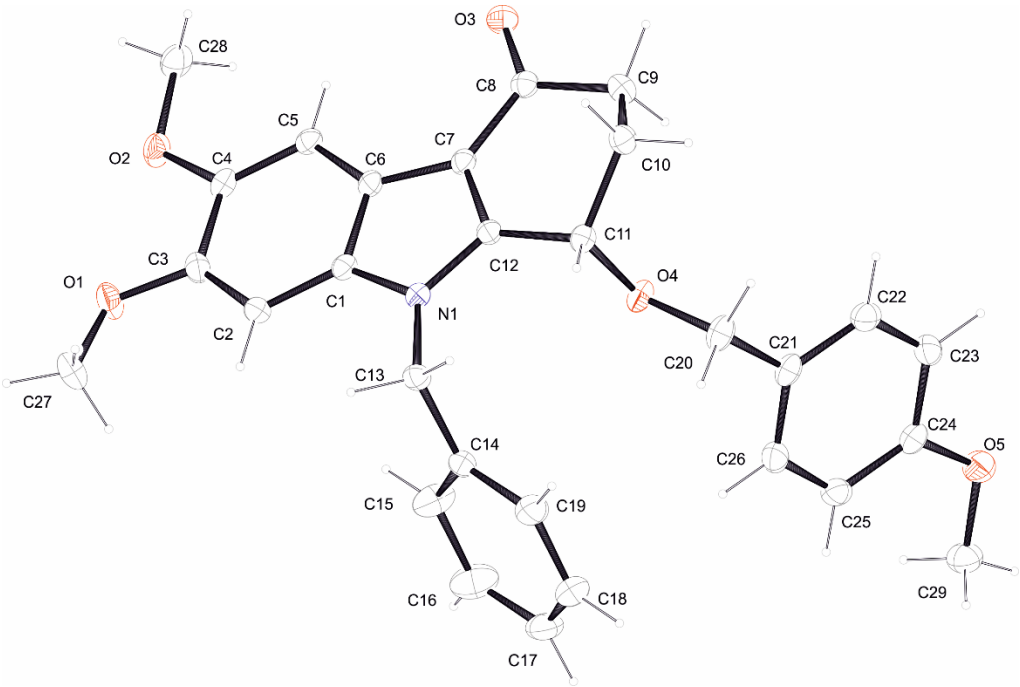
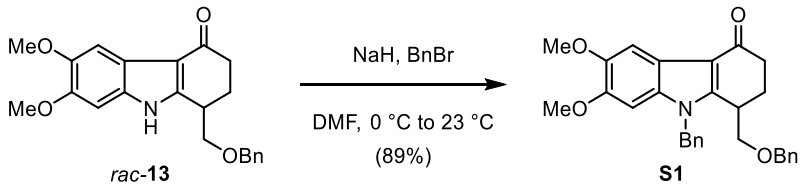


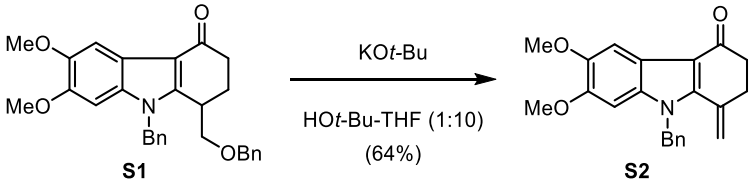
Figure S1. Molecular structure of tetrahydrocarbazolone **33**. Displacement ellipsoids are drawn at the 50% probability level.

II. Experimental Procedures



Scheme S1. Synthesis of *N*-benzyltetrahydrocarbazolone **S1**.

***N*-Benzyltetrahydrocarbazolone S1**. To a solution of tetrahydrocarbazolone *rac*-**13** (90 mg, 0.25 mmol, 1 equiv) in *N,N*-dimethylformamide (1.2 mL) was added sodium hydride (15 mg, 0.37 mmol, 1.5 equiv, 60% dispersion in mineral oil) at 0 °C. After 30 min, benzyl bromide (51 mg, 0.30 mmol, 1.5 equiv) was added and the solution was allowed to warm to 23 °C. After 2 h, the solution was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **S1** as a white foam (100 mg, 89%). TLC (50% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.70 (s, 1H), 7.36–7.20 (m, 8H), 7.02–6.93 (m, 2H), 6.65 (s, 1H), 5.49 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 4.48–4.38 (m, 2H), 3.89 (s, 3H), 3.73 (s, 4H), 3.72–3.68 (m, 1H), 3.61 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.41–3.30 (m, 1H), 2.66 (ddd, *J* = 18.3, 13.6, 5.4 Hz, 1H), 2.45–2.20 (m, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 193.9, 150.8, 148.1, 147.7, 138.6, 137.2, 131.9, 129.4, 128.9, 128.2, 128.1, 126.5, 118.2, 113.2, 103.7, 94.7, 73.7, 71.5, 56.7, 56.6, 47.9, 34.5, 33.5, 27.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1728, 1640, 1584, 1526, 1494, 1481, 1450, 1359, 1333, 1308, 1269, 1207, 1194, 1157, 1104, 1071 cm^{-1}. HR-MS (ESI): calcd for $(C_{29}H_{30}O_4N)^+$ $(M+H)^+$: 456.2175, found: 456.2164.

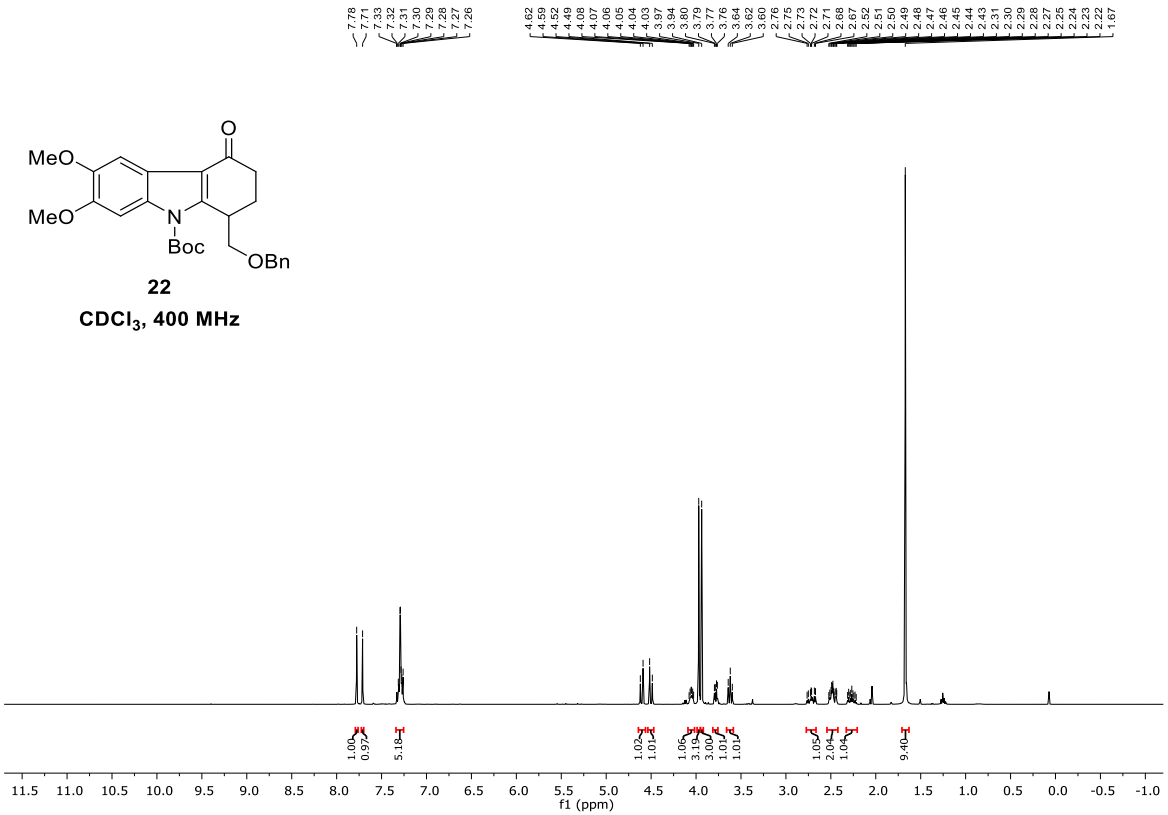


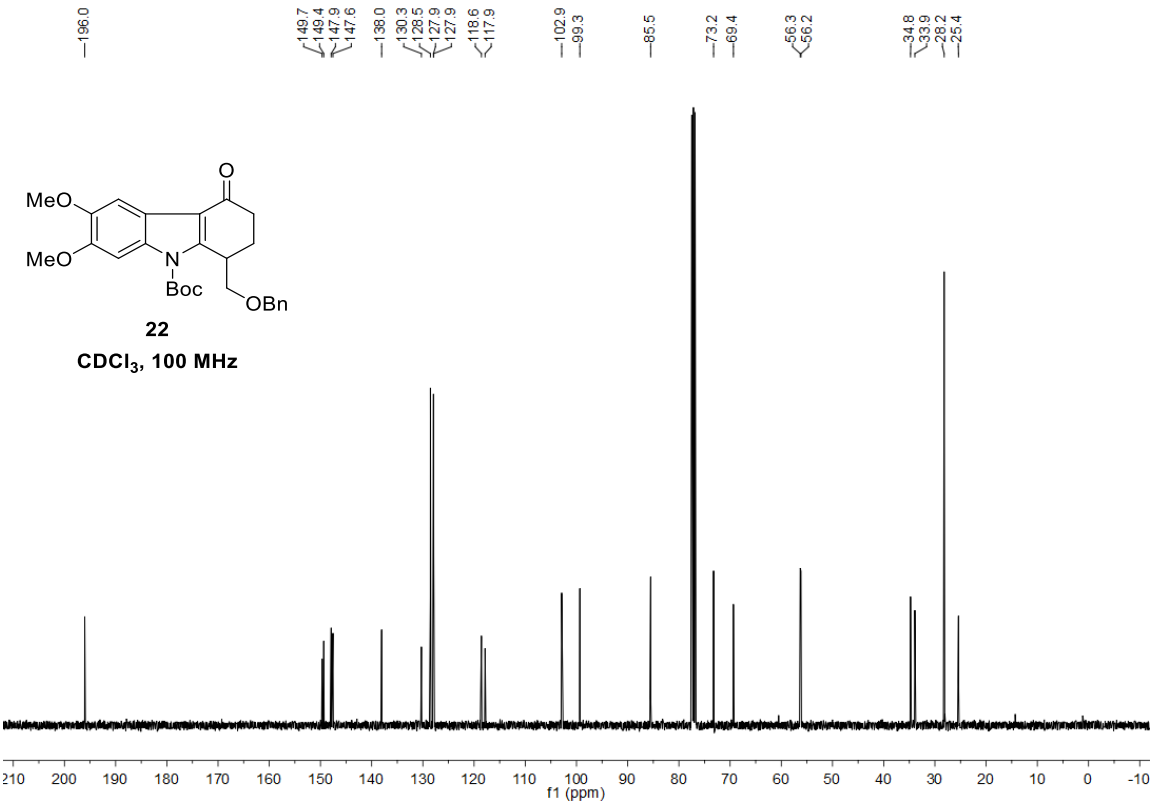
Scheme S2. Synthesis of elimination product **S2**.

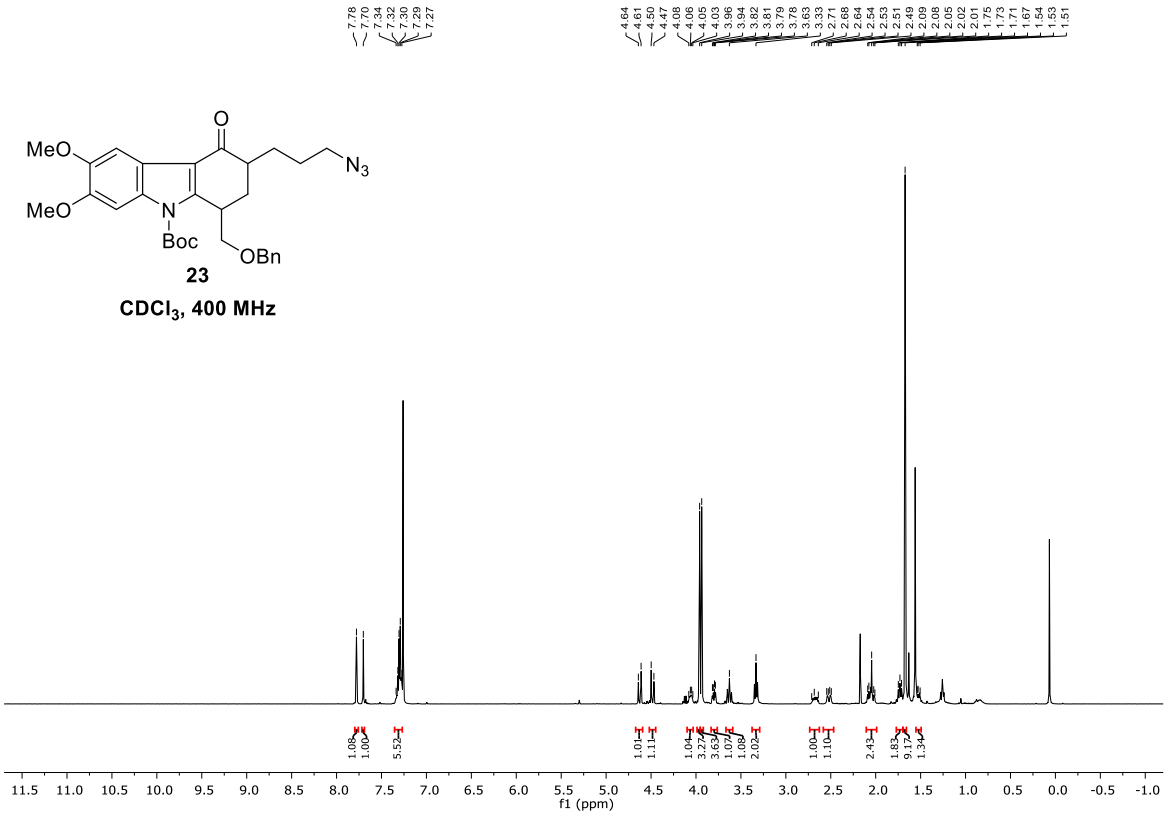
Elimination Product S2. To a solution *N*-benzyltetrahydrocarbazolone **S1** (17.5 mg, 38.4 µmol, 1 equiv) in tetrahydrofuran (0.3 mL) and *tert*-butanol (30 µL) was added potassium *tert*-butoxide

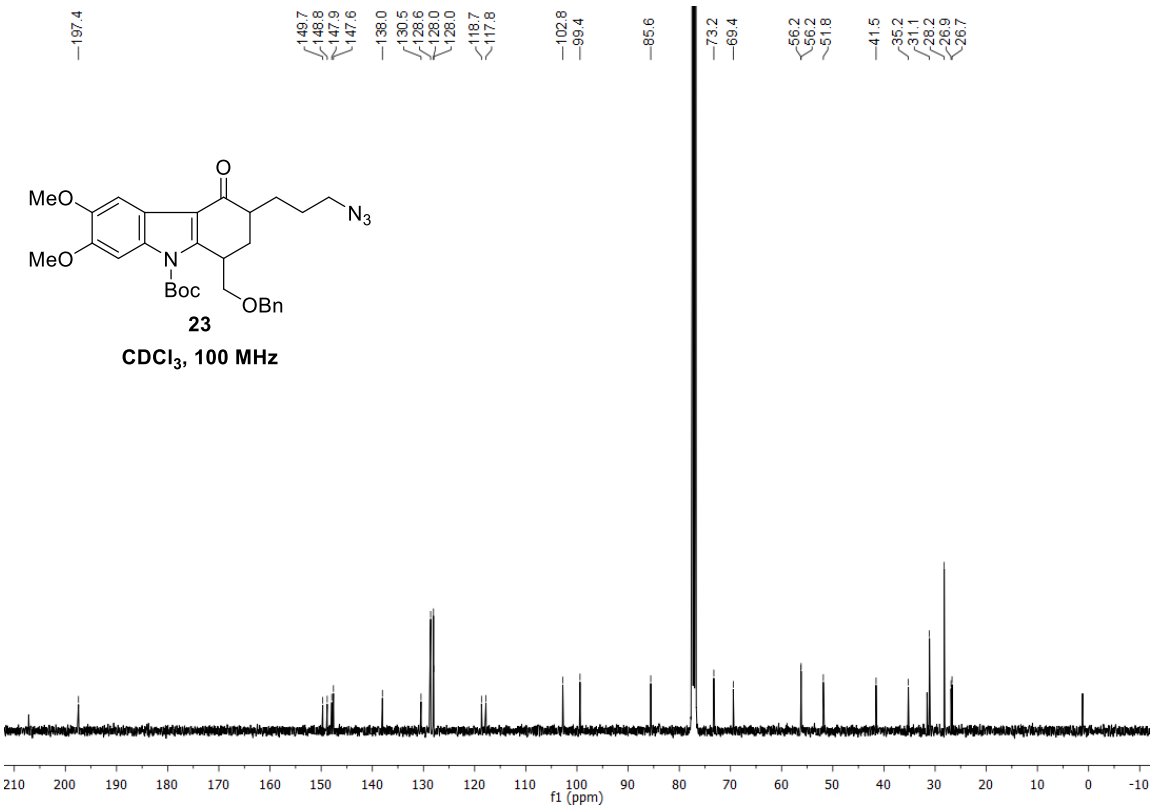
(15.1 mg, 0.134 mmol, 3.50 equiv) at 0 °C and the solution was allowed to warm to 23 °C. After 1 h, the solution was diluted with saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **S2** as a brown solid (8.5 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.39–7.29 (m, 3H), 7.13–7.07 (m, 2H), 6.64 (s, 1H), 5.51 (s, 2H), 5.34 (s, 1H), 5.13 (s, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 2.86 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 6.5 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 148.8, 147.6, 145.1, 136.5, 135.1, 133.6, 129.3, 127.9, 125.8, 117.5, 114.3, 113.1, 103.4, 93.3, 56.5, 56.3, 48.7, 39.4, 35.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2945, 1646, 1559, 1497, 1480, 1448, 1360, 1270, 1194, 1141, 1095, 1027 cm^{-1}. HR-MS (ESI): calcd for $(C_{22}H_{22}O_3N)^+$: 348.1600, found: 348.1591.

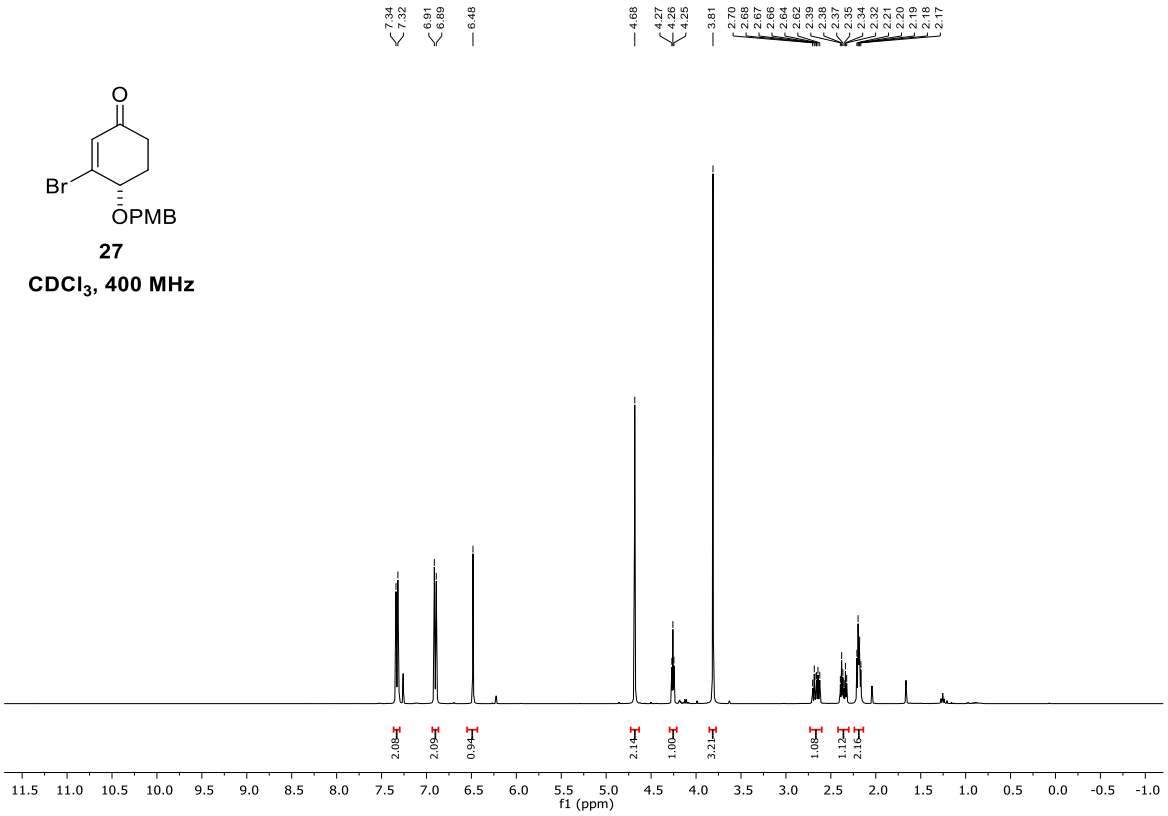
III. ^{1}H NMR and ^{13}C NMR spectra





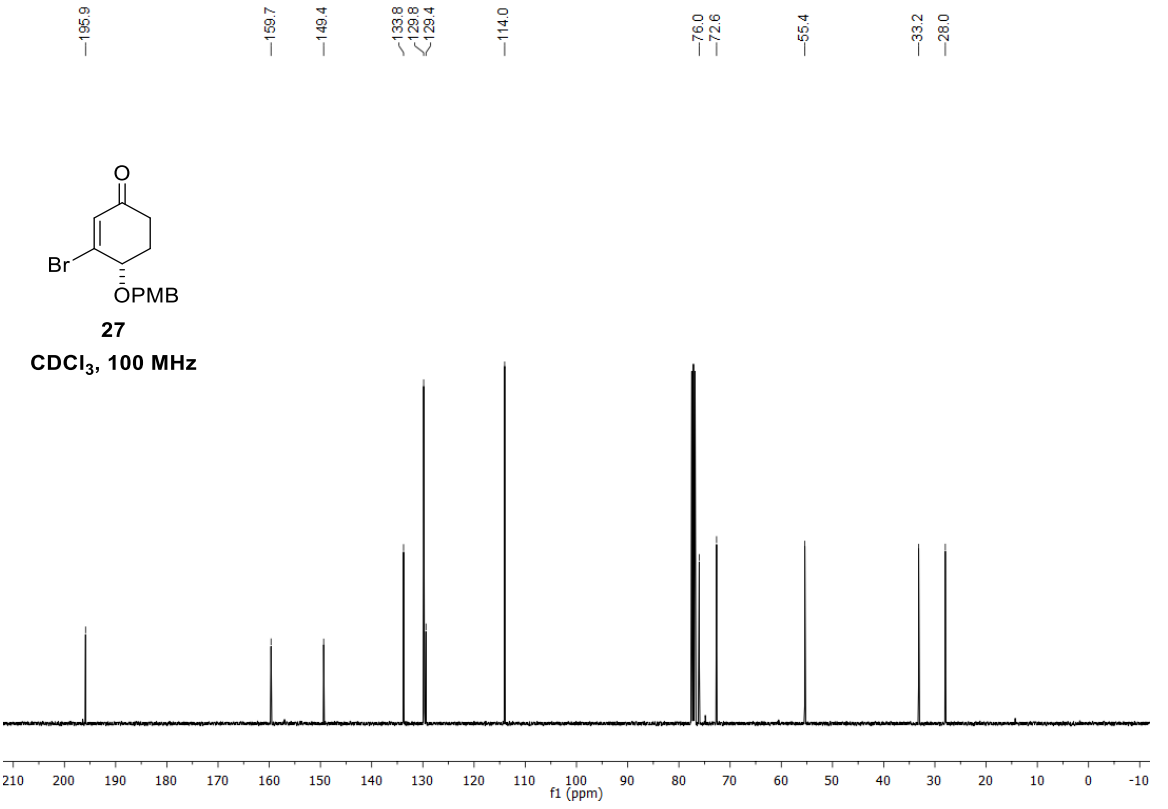

MeO
MeO
O
N
Boc
OBn
N3
23
CDCl3, 400 MHz
f1 (ppm)


MeO
MeO
O
N
Boc
OBn
N3
23
CDCl3, 100 MHz
f1 (ppm)



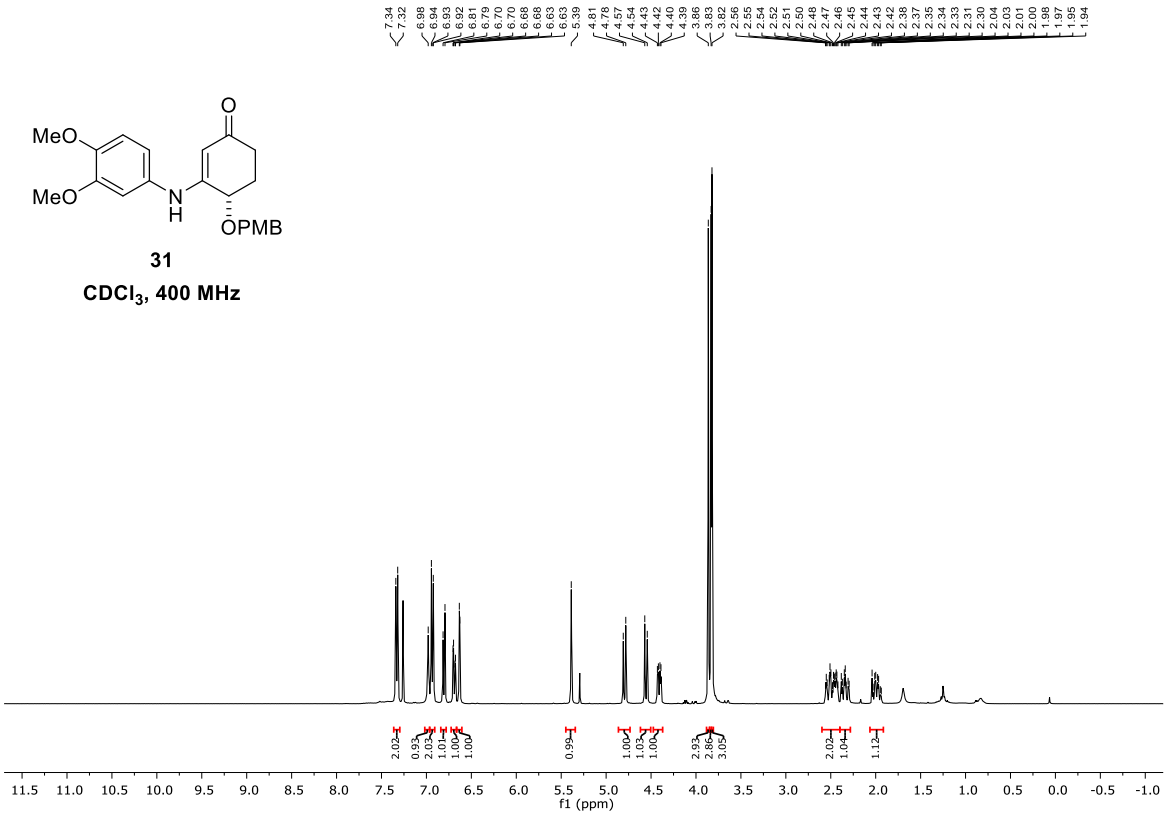
27

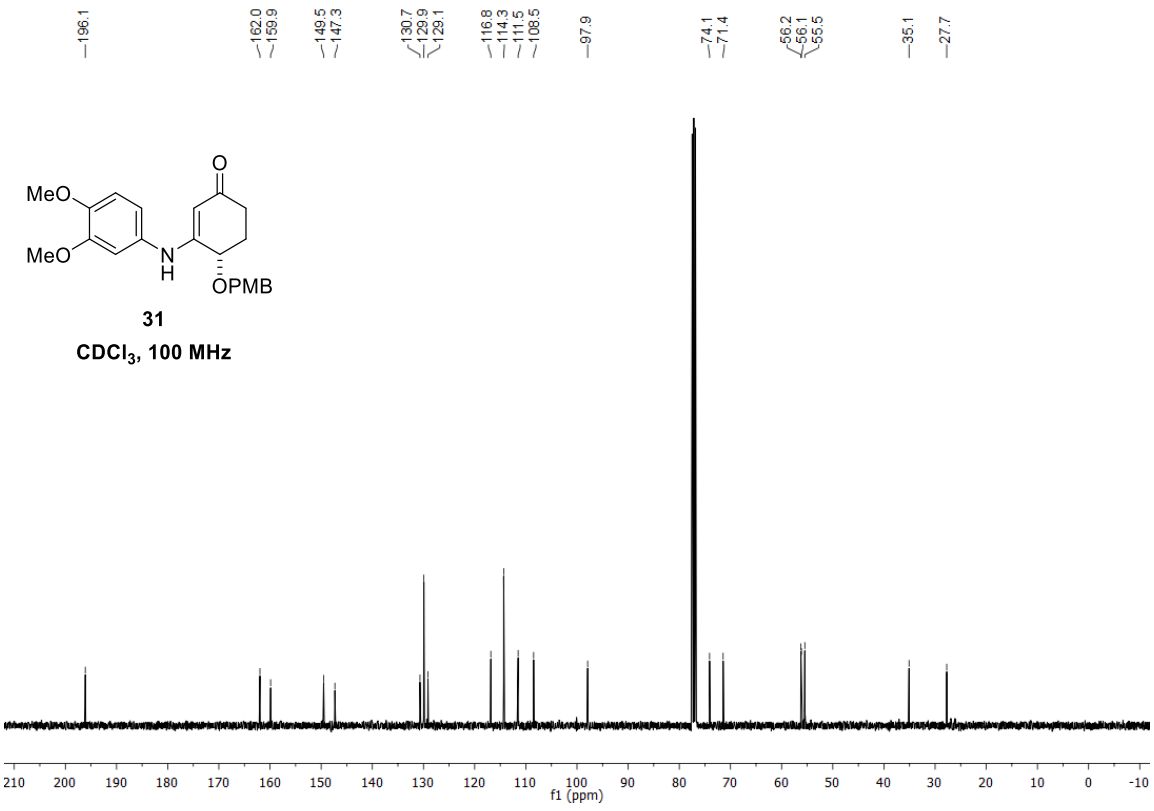
$CDCl_3$, 400 MHz

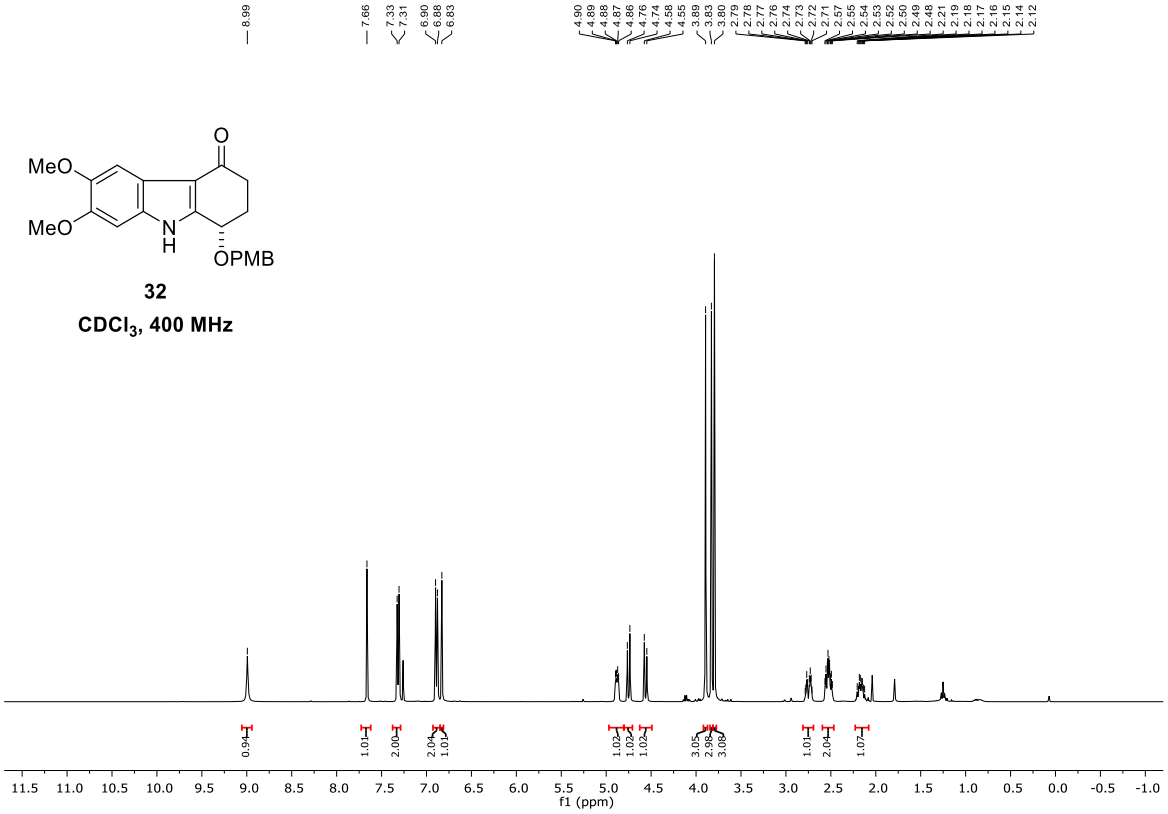


27

$CDCl_3$, 100 MHz

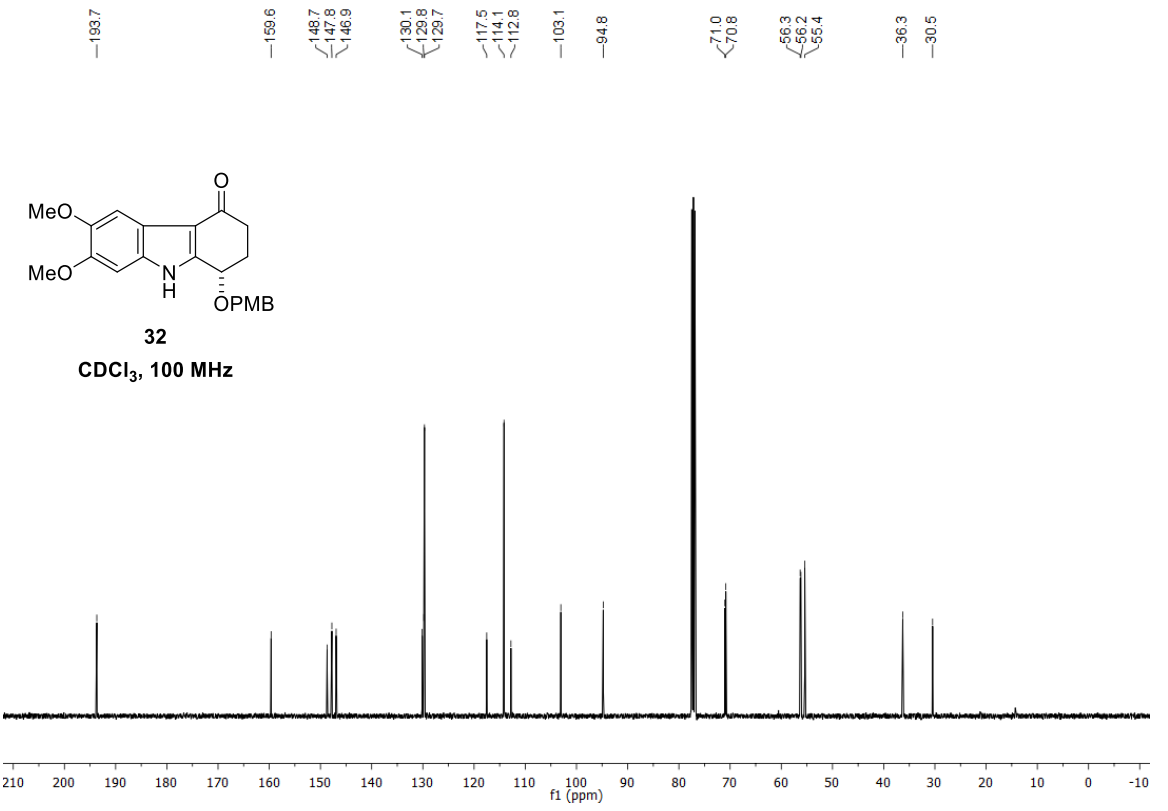

MeO
MeO
N
H
O
OPMB
31
CDCl3, 400 MHz
f1 (ppm)


MeO
MeO
N
H
O
OPMB
31
CDCl3, 100 MHz
f1 (ppm)



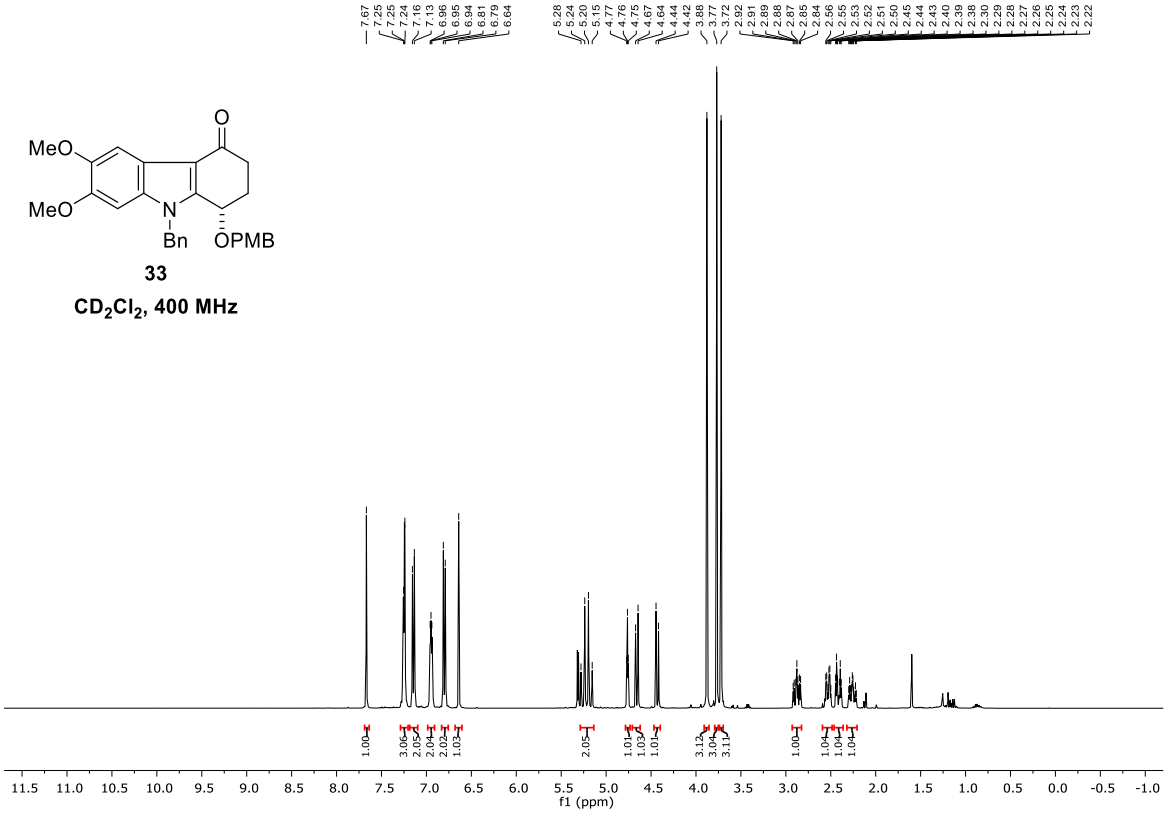
32

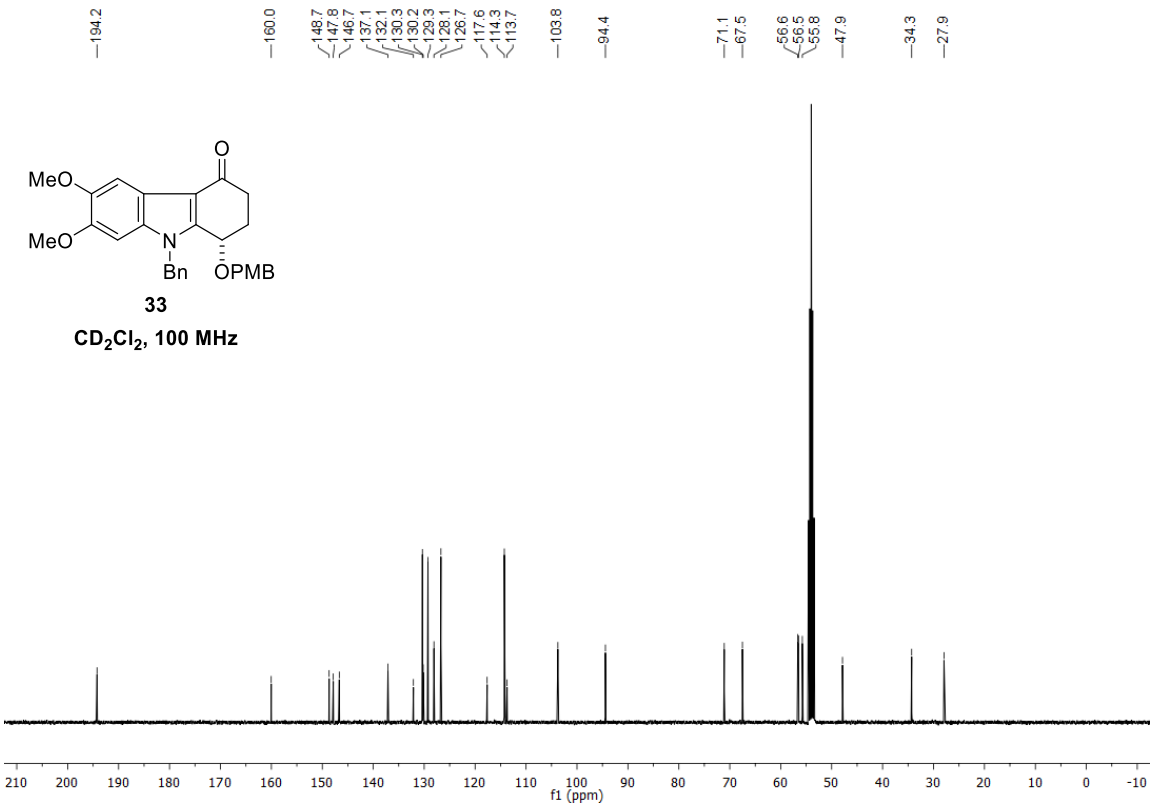
$CDCl_3$, 400 MHz

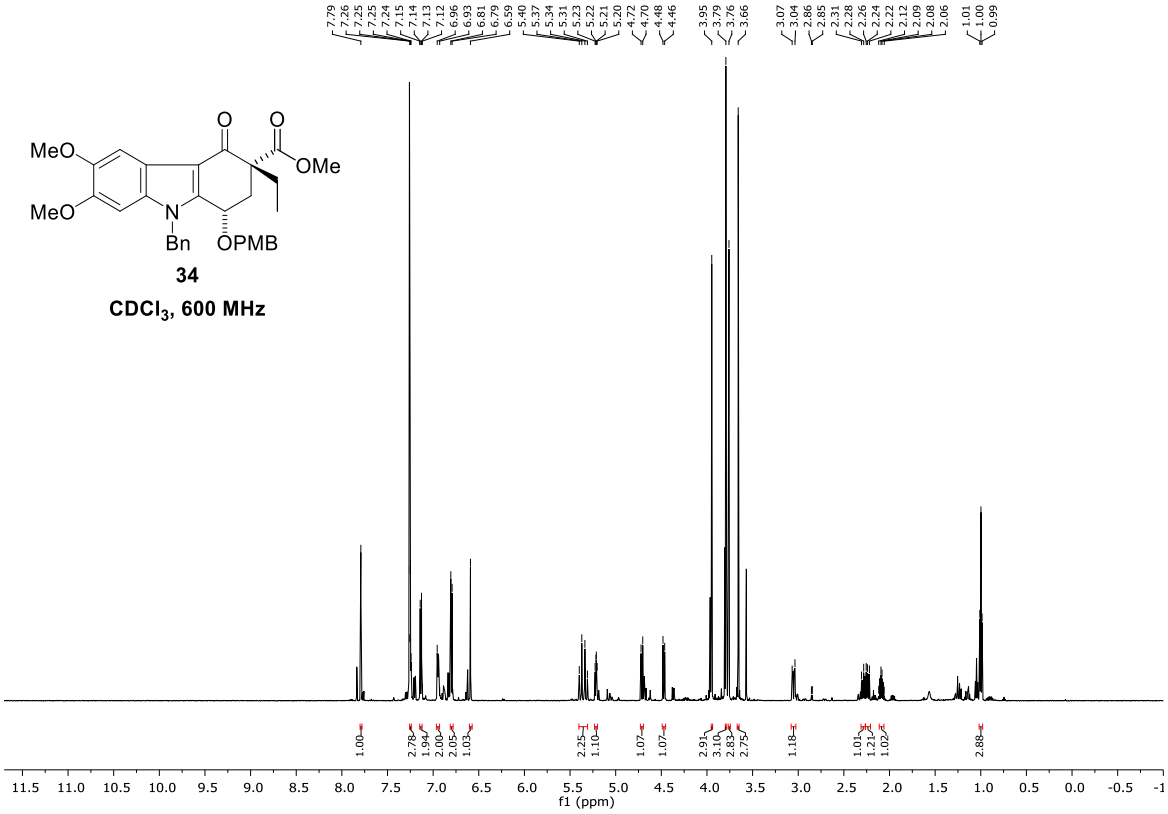


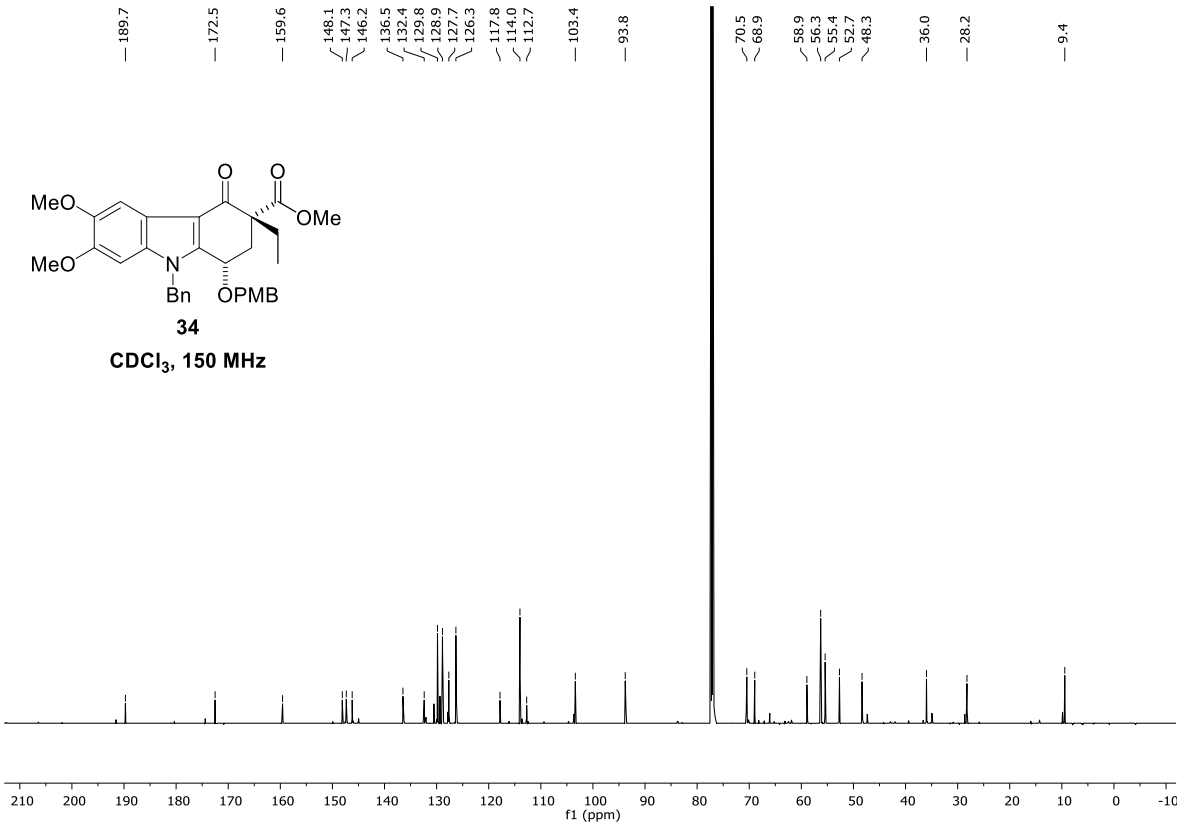
32

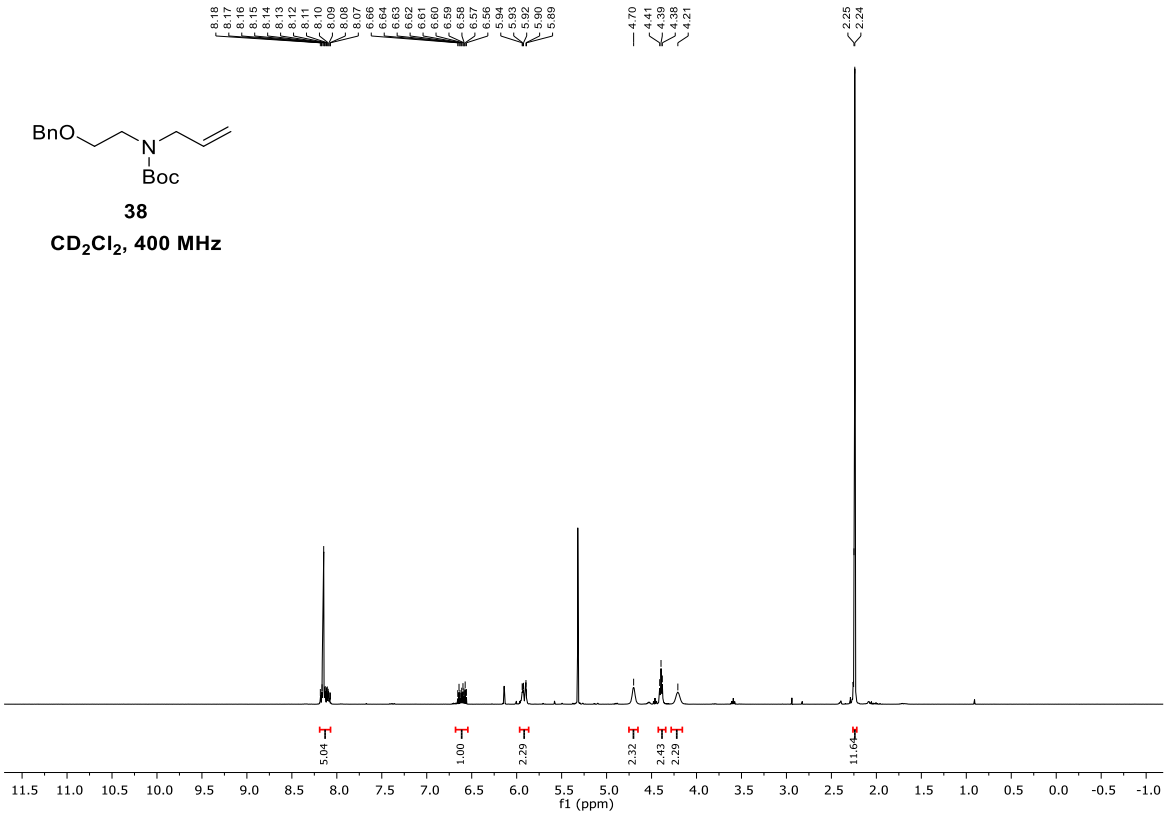
$CDCl_3$, 100 MHz


MeO
MeO
O
N
Bn
OPMB
33
CD2Cl2, 400 MHz
f1 (ppm)


MeO
MeO
O
N
Bn
OPMB
33
CD2Cl2, 100 MHz
f1 (ppm)

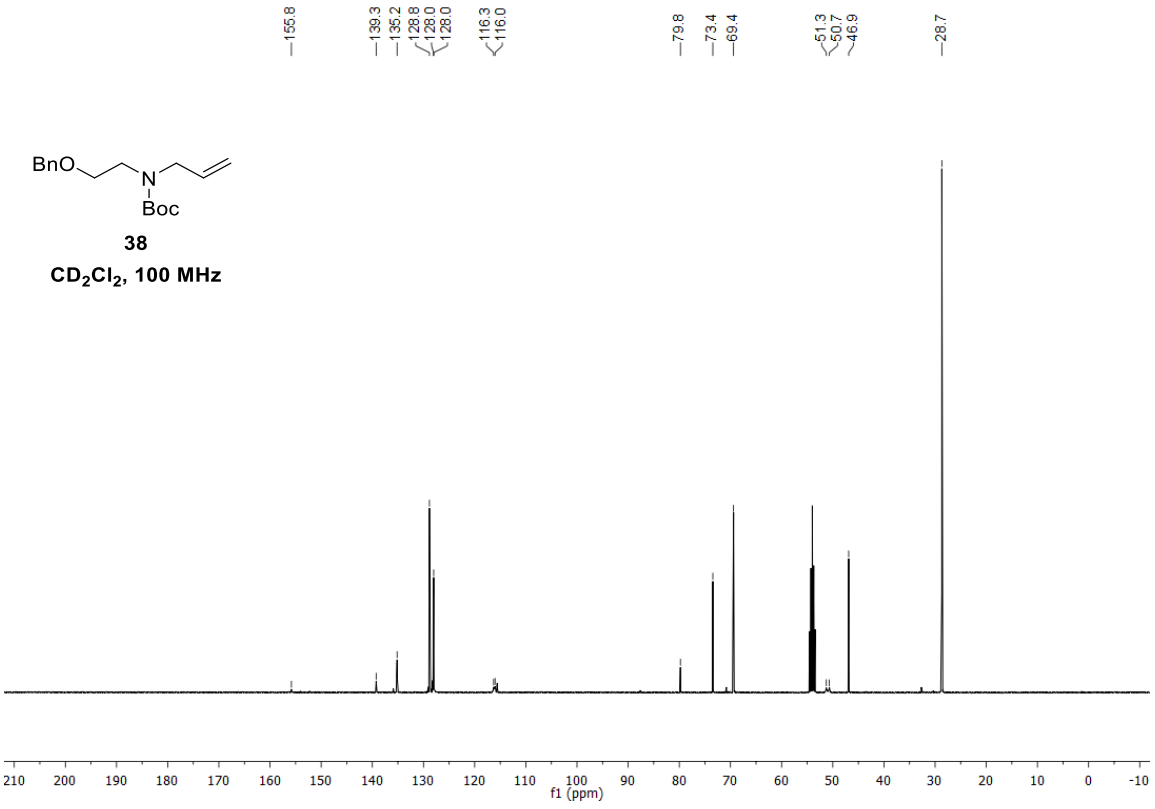

MeO
MeO
O
O
OMe
N
Bn
OPMB
34
CDCl3, 600 MHz
f1 (ppm)


MeO
MeO
O
O
OMe
N
Bn
OPMB
34
CDCl3, 150 MHz
f1 (ppm)



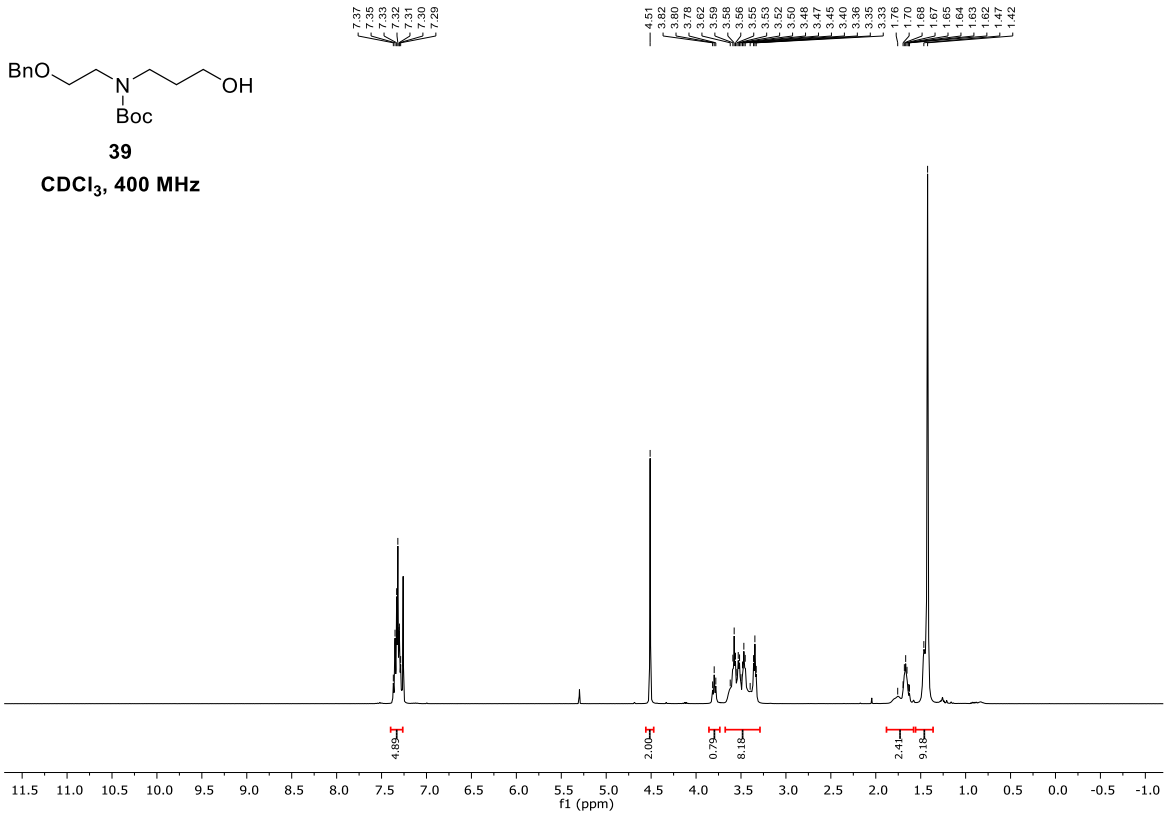
38

CD_2Cl_2, 400 MHz



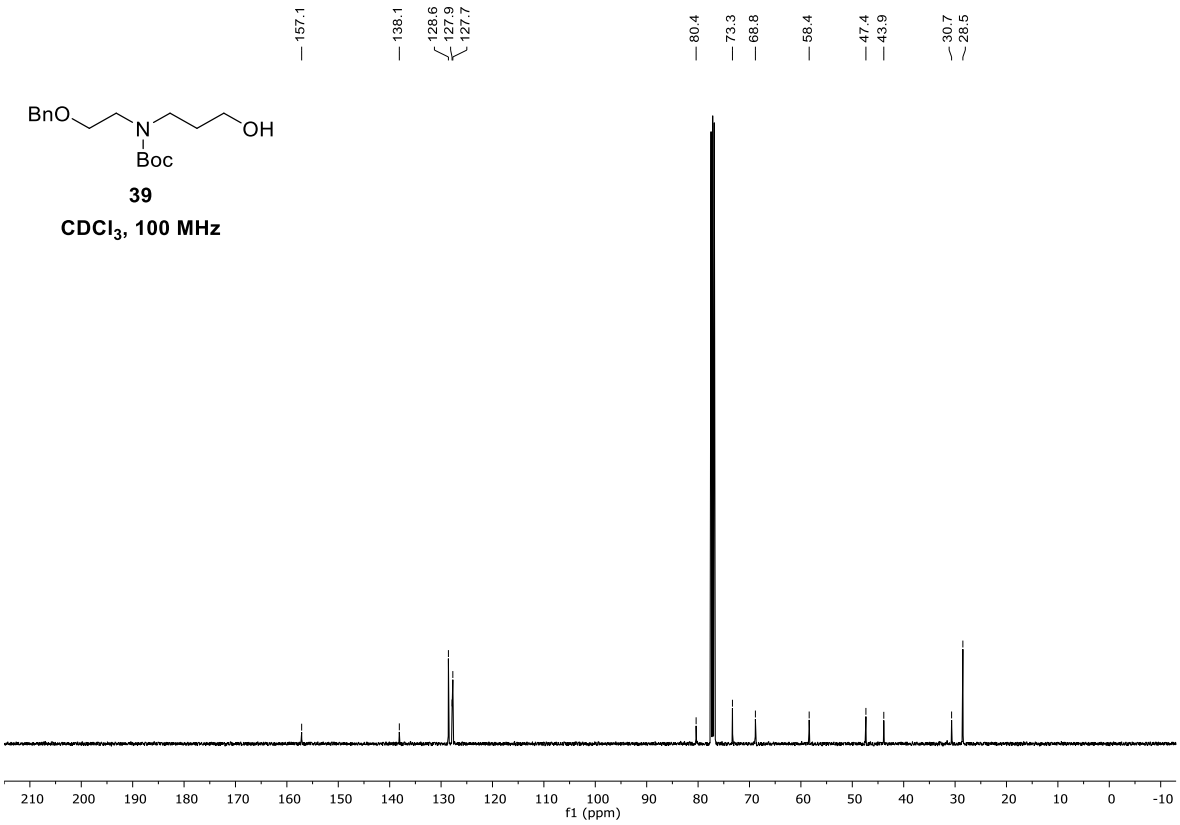
38

CD_2Cl_2, 100 MHz



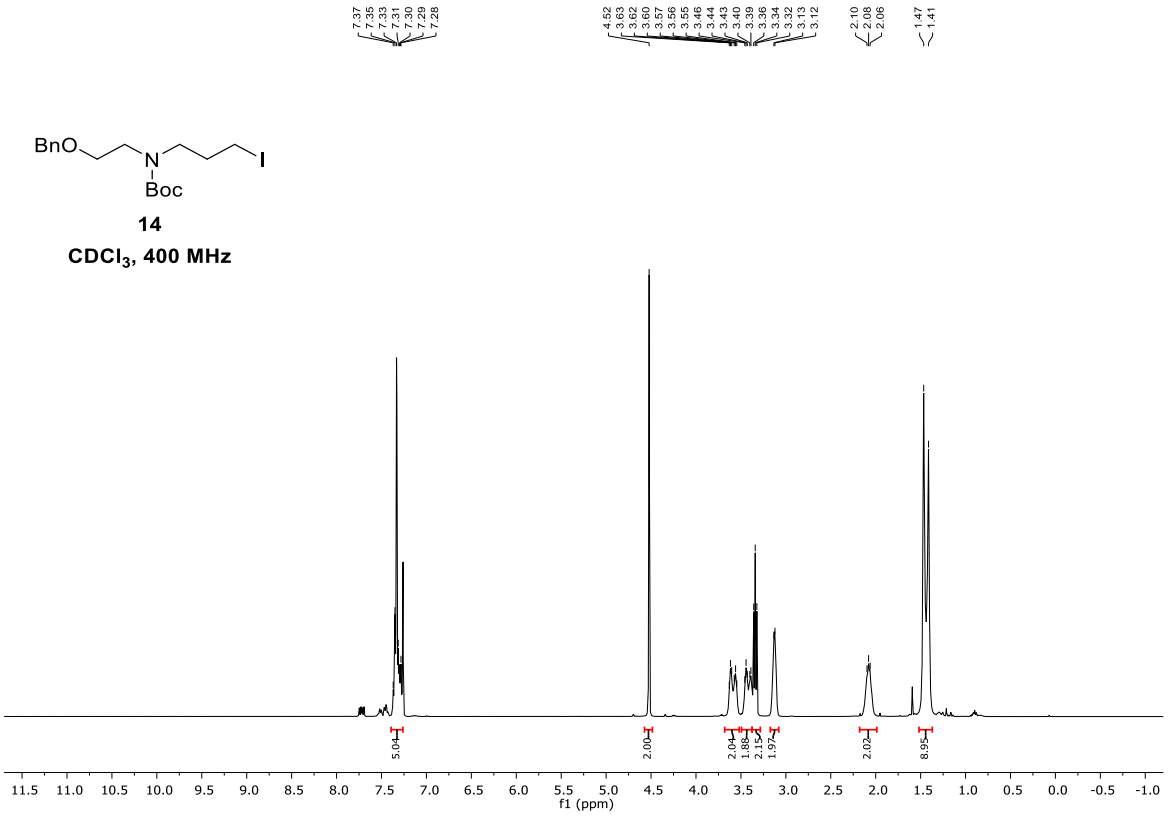
39

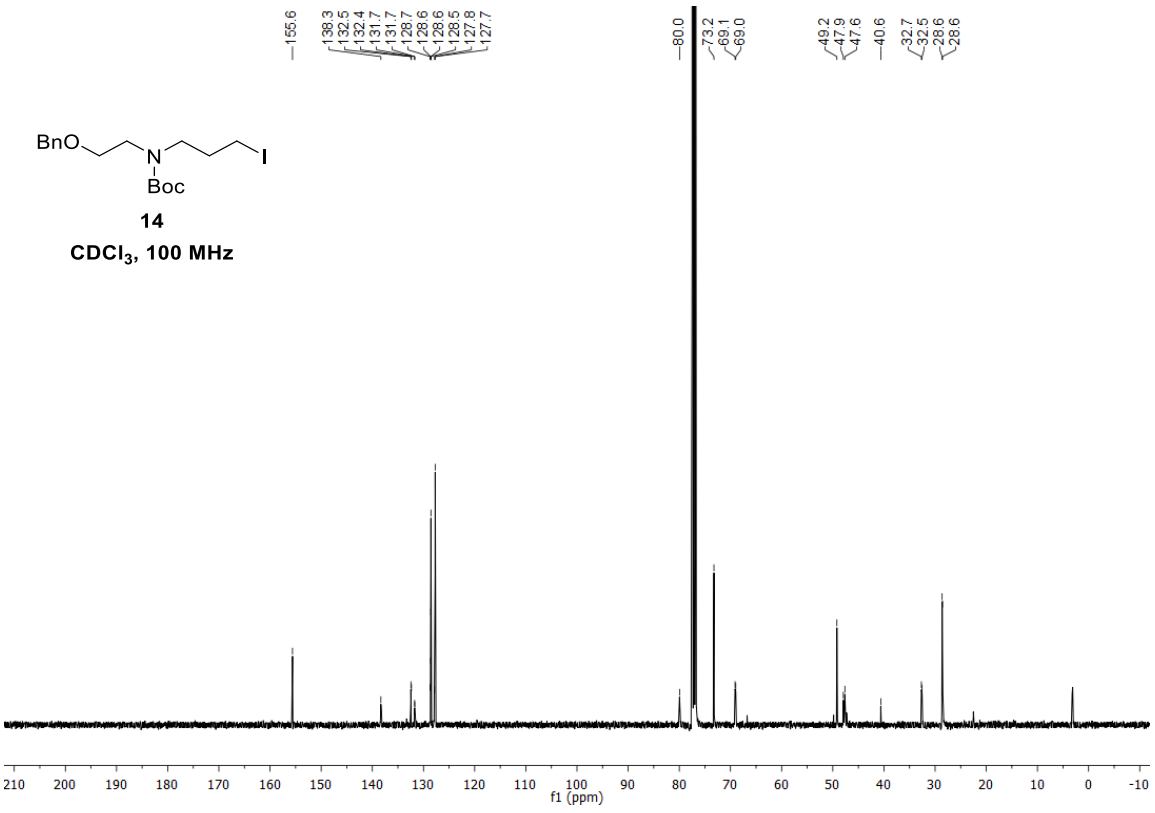
$CDCl_3$, 400 MHz

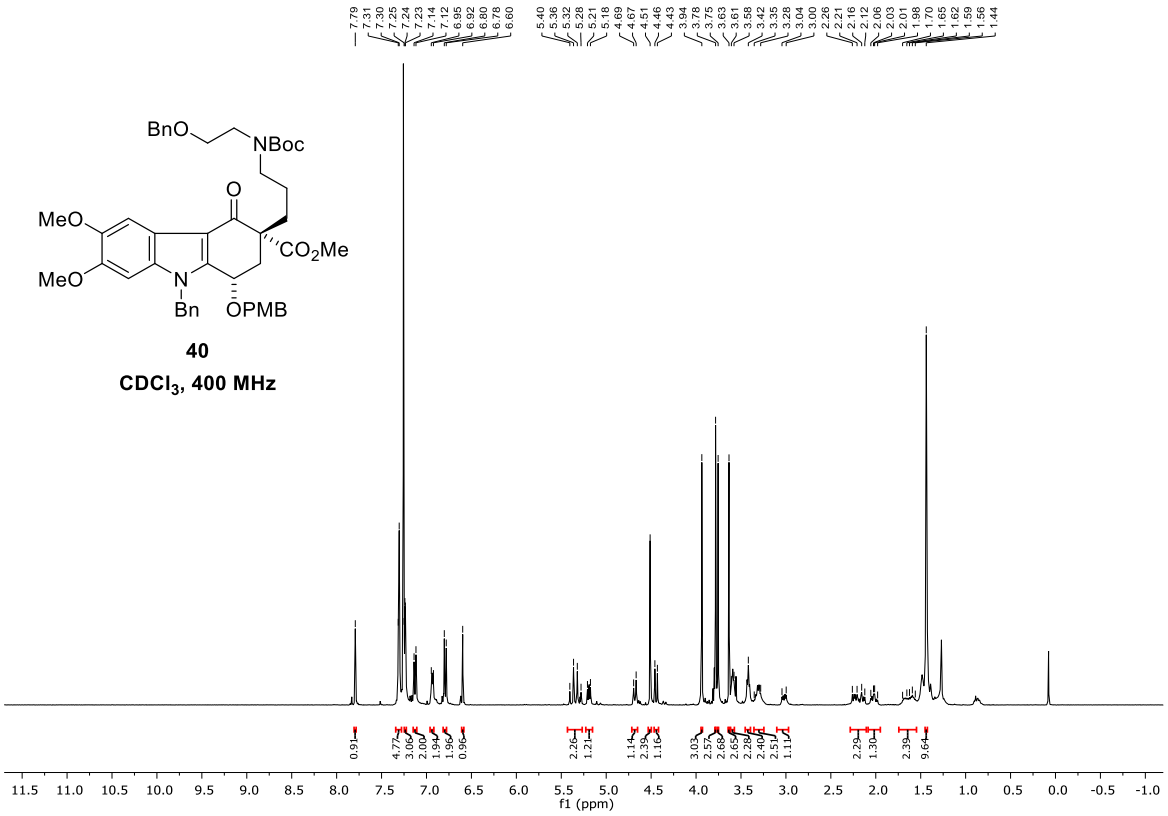


39

$CDCl_3$, 100 MHz

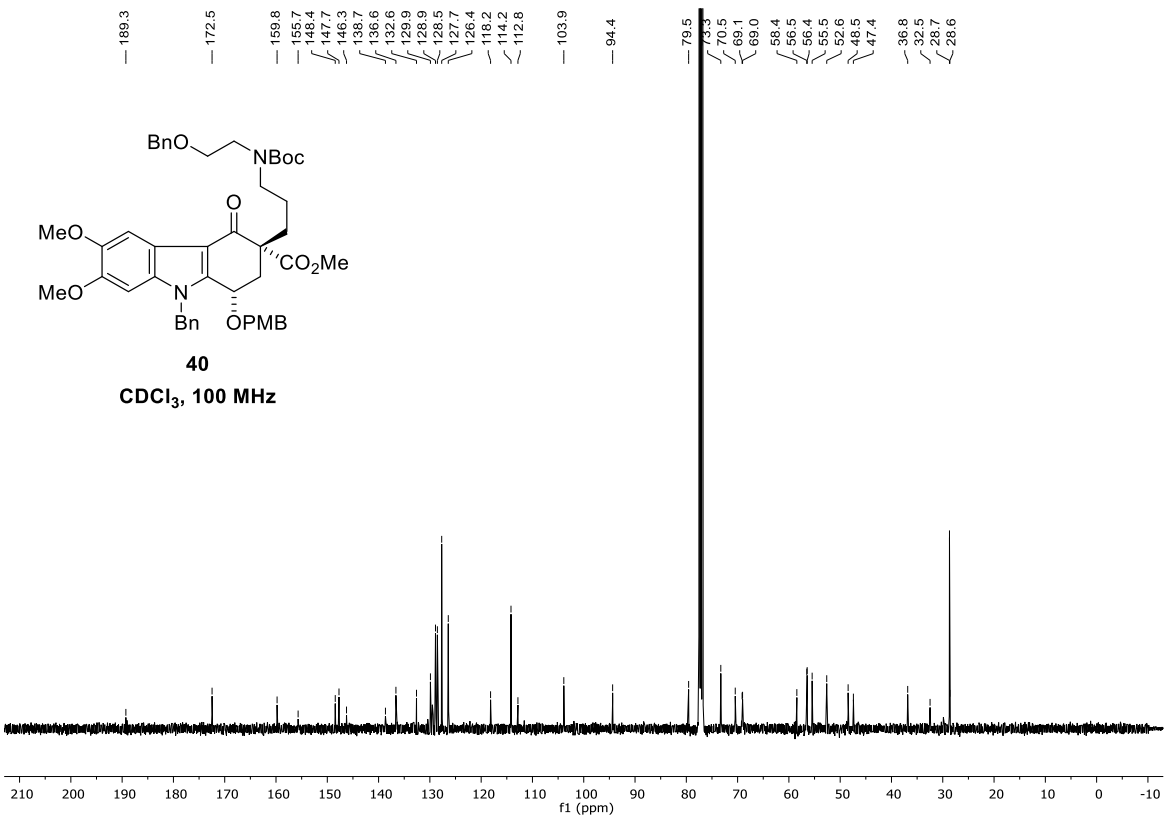

BnO
N
Boc
I
14
CDCl3, 400 MHz
f1 (ppm)


BnO
N
Boc
I
14
CDCl3, 100 MHz
f1 (ppm)



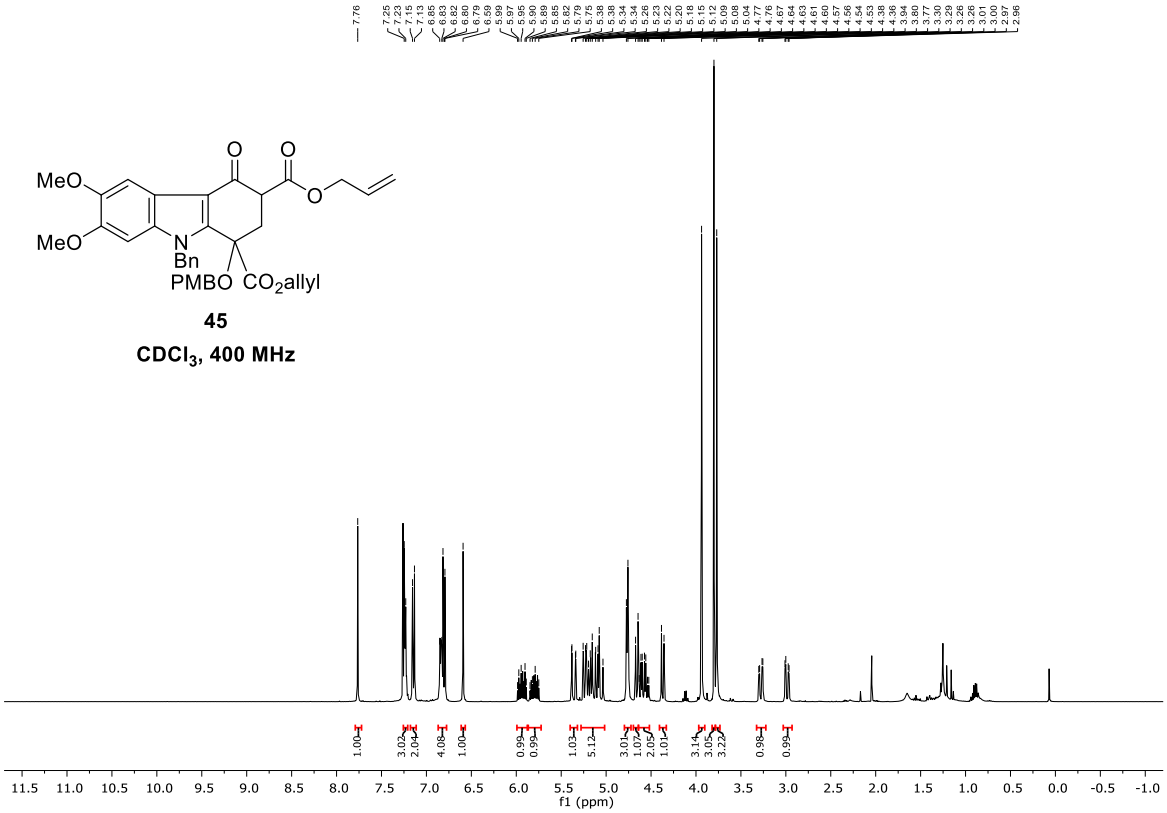
40

$CDCl_3$, 400 MHz



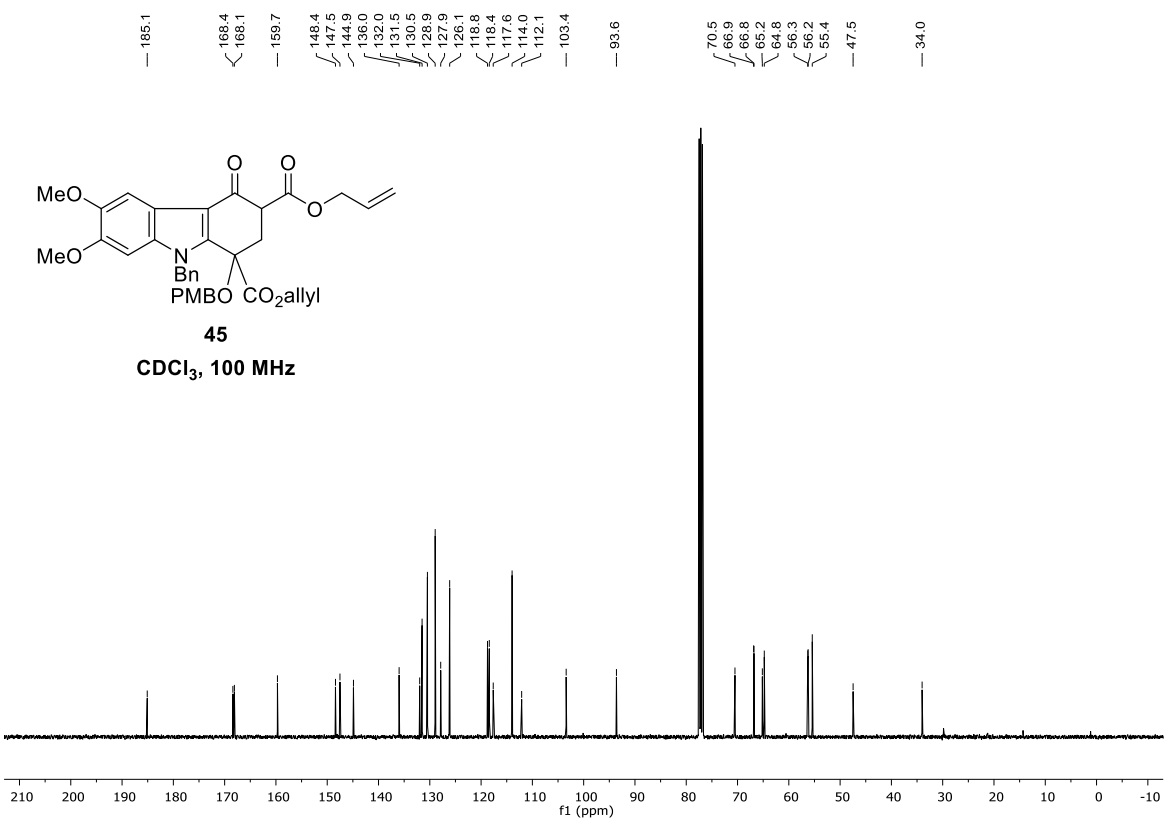
40

$CDCl_3$, 100 MHz



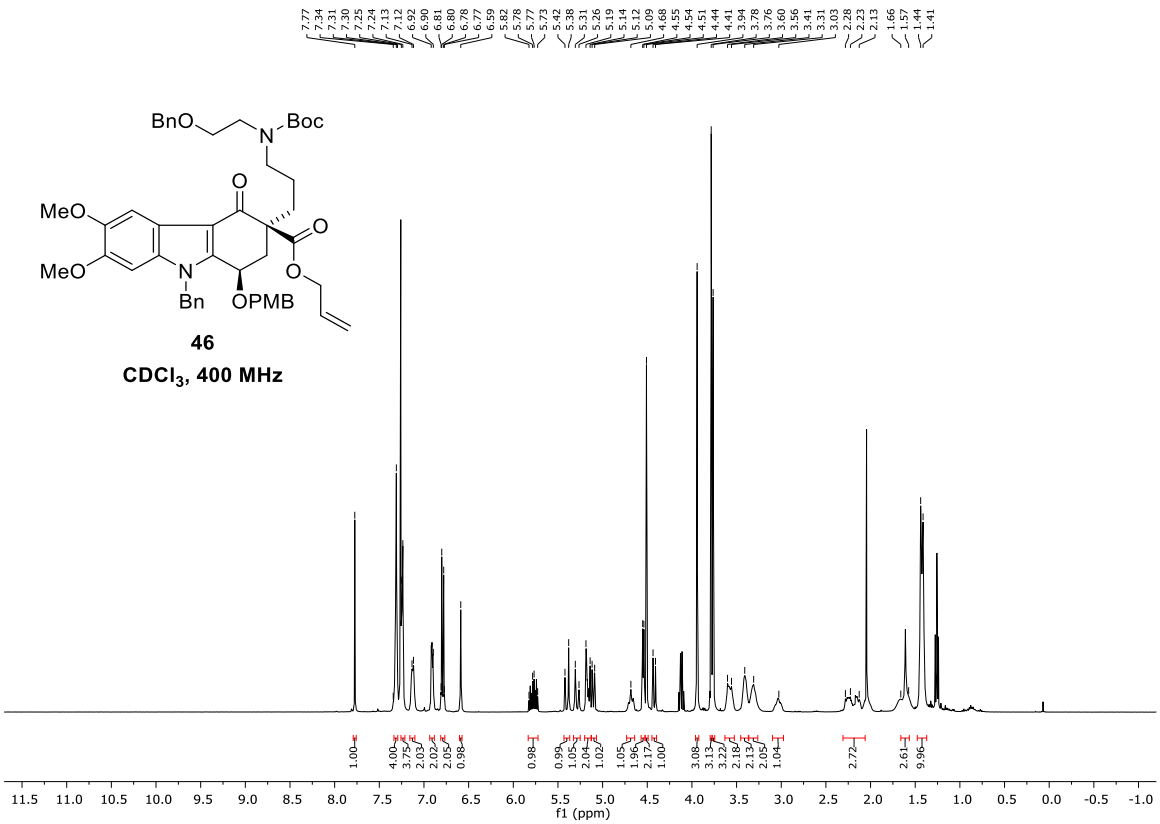
45

$CDCl_3$, 400 MHz



45

$CDCl_3$, 100 MHz



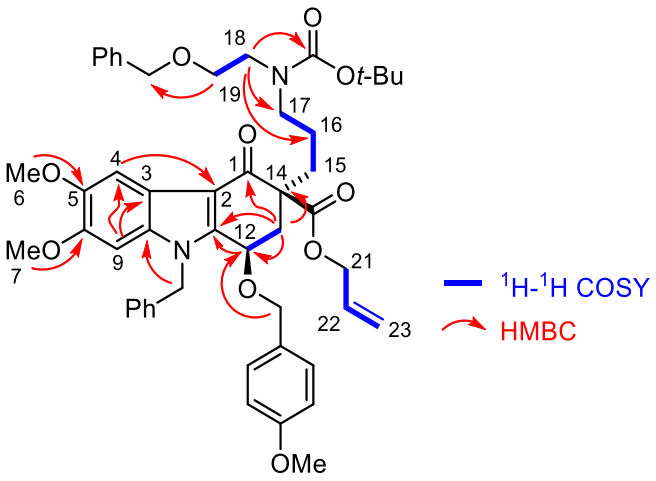
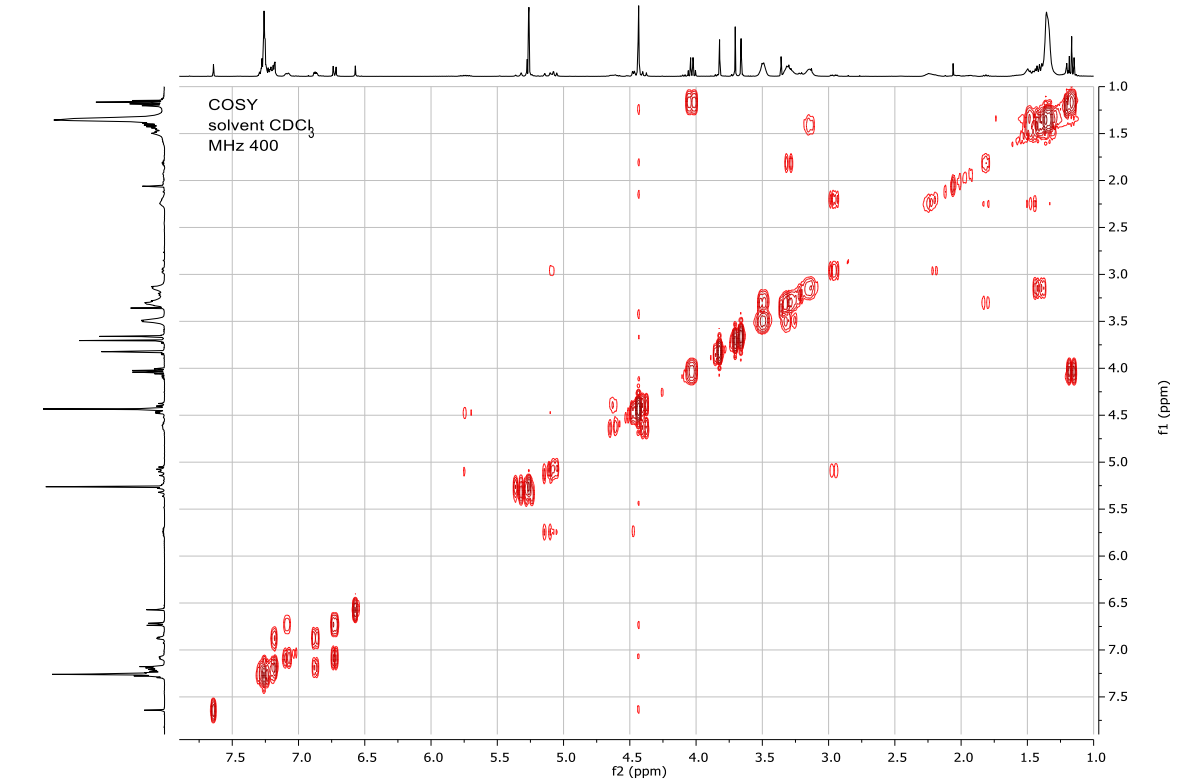
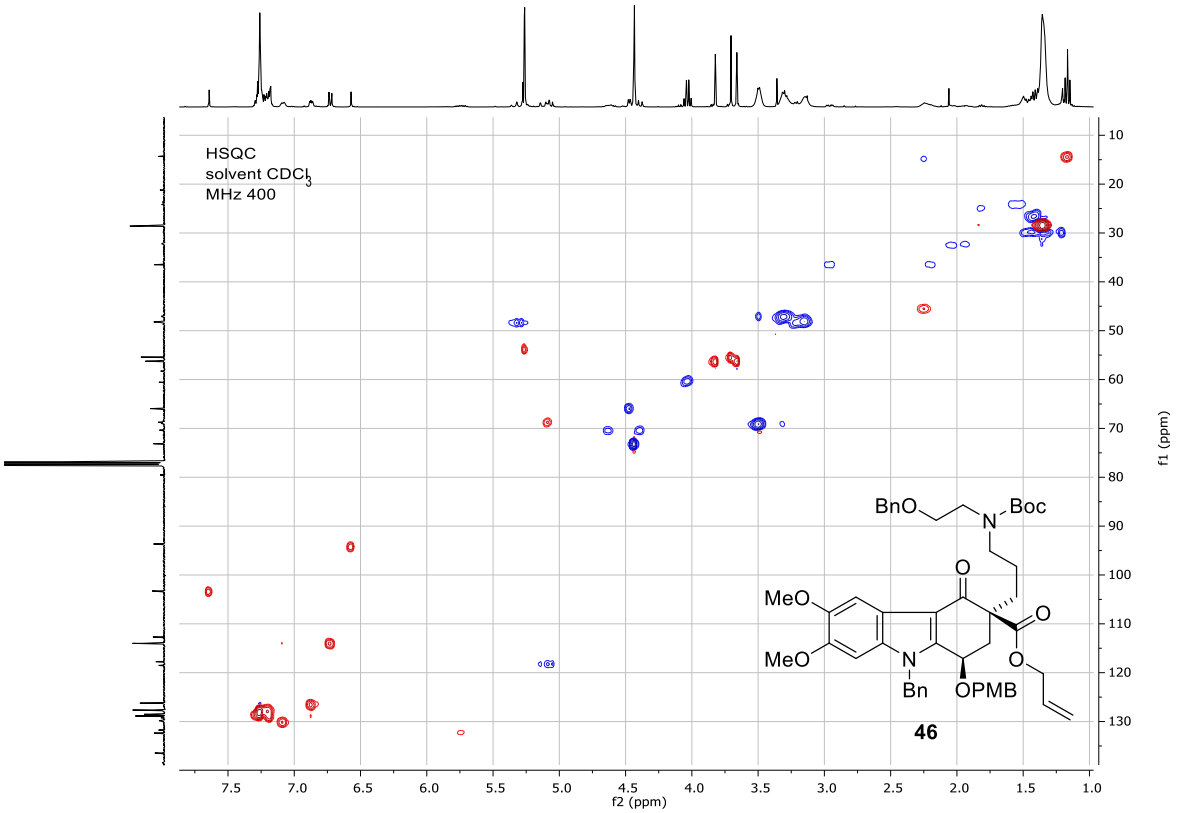
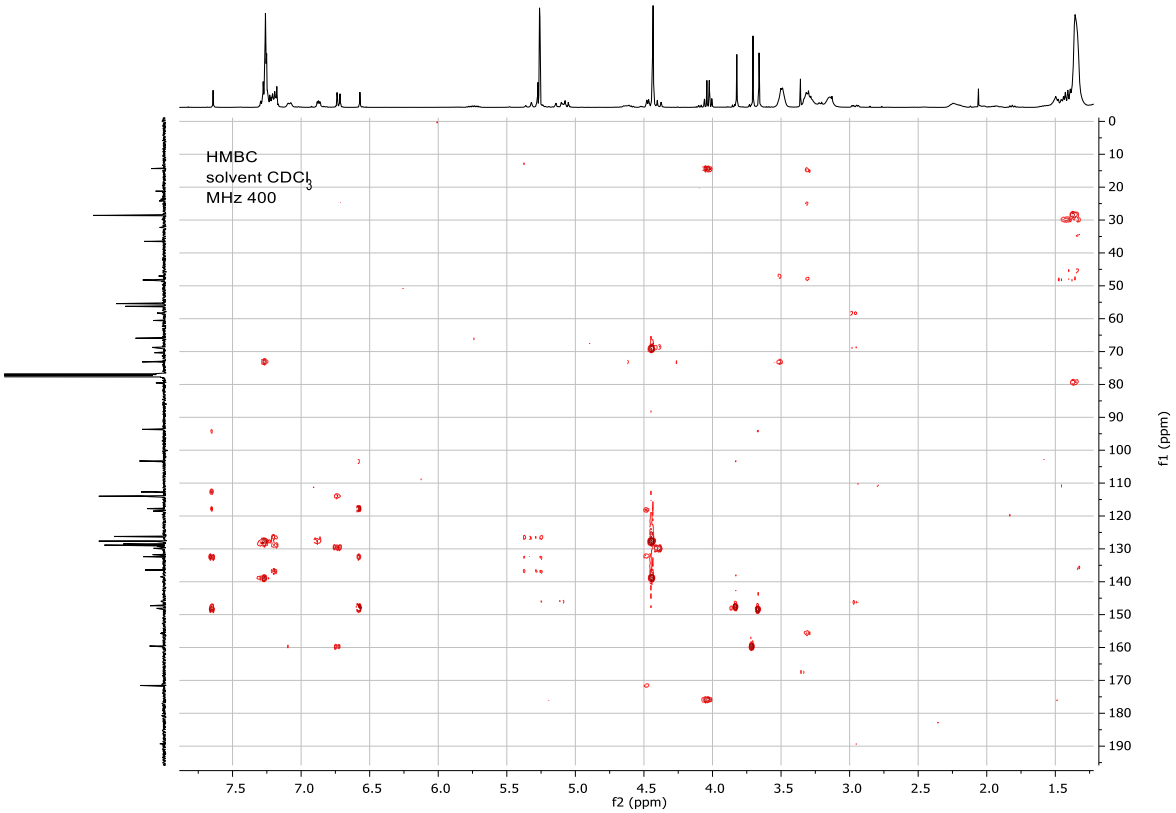
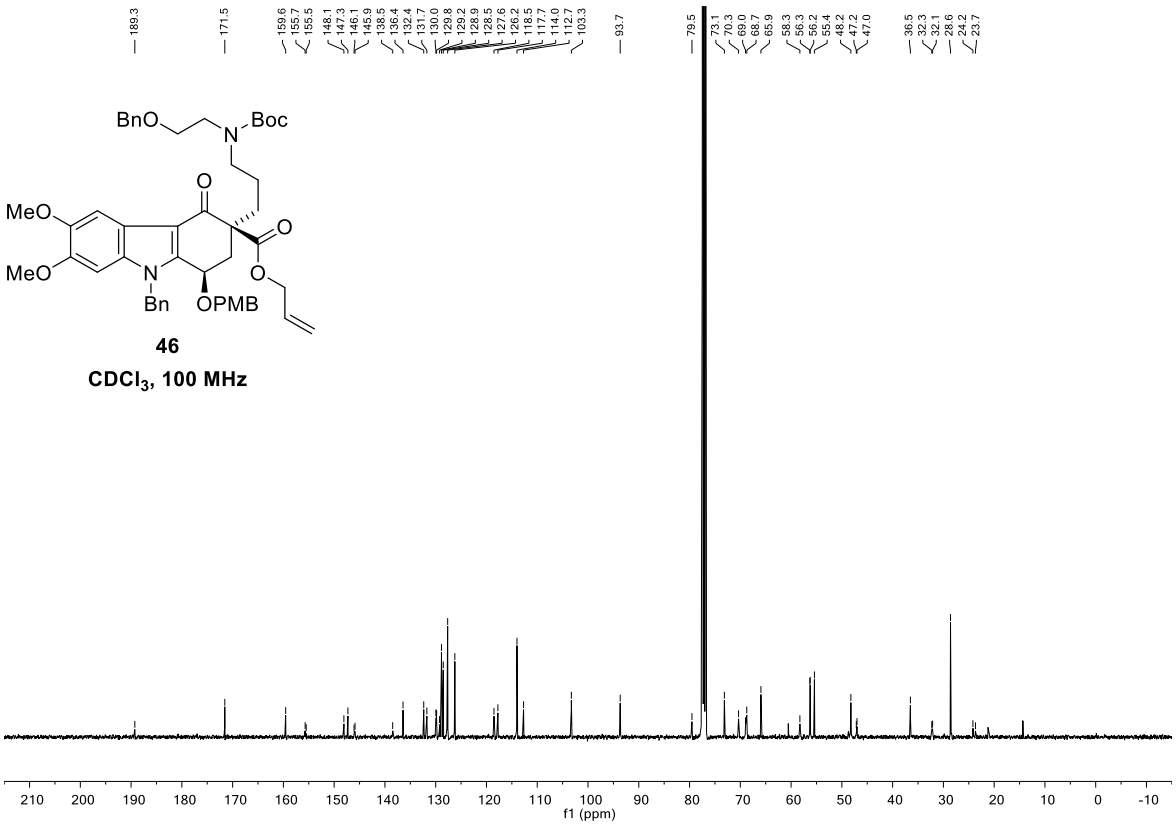


Figure S2. Key ^{1}H-^{1}H COSY and HMBC correlations of **46**.


COSY
solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

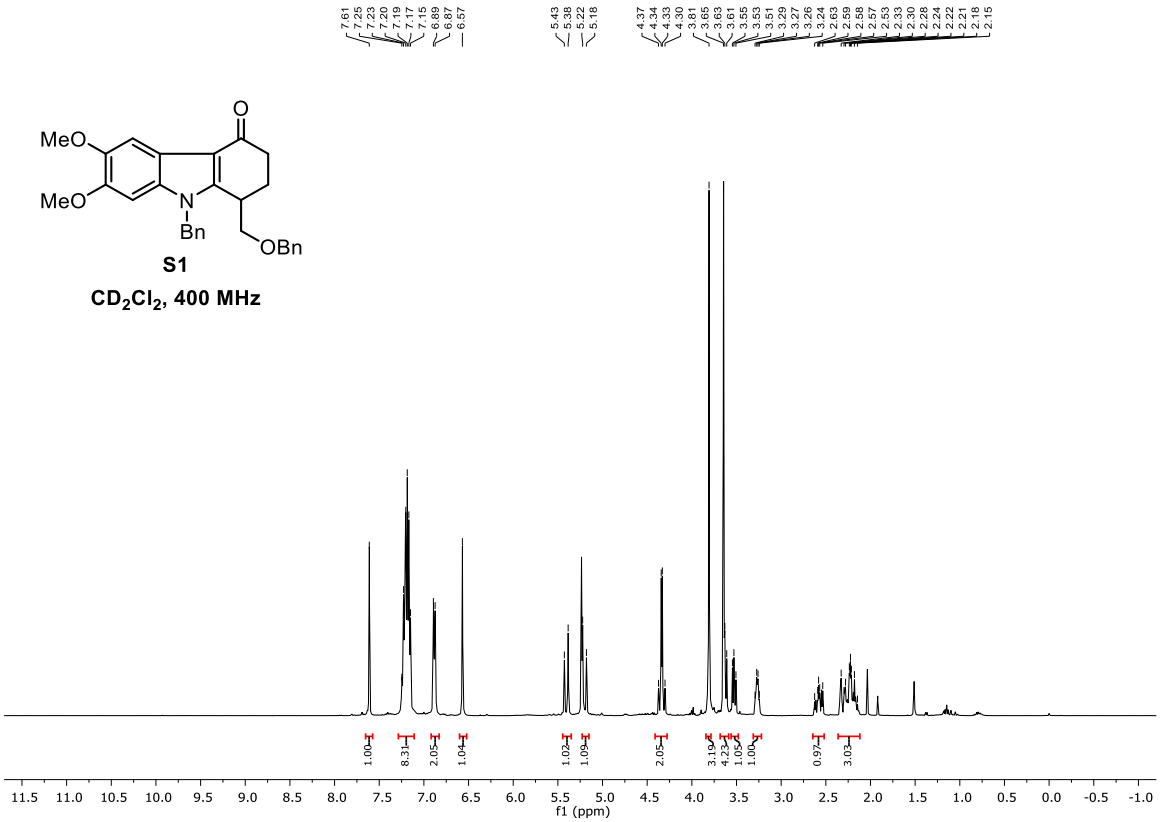

HSQC
solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)
BnO
N
Boc
MeO
MeO
N
Bn
OPMB
O
O
O
46

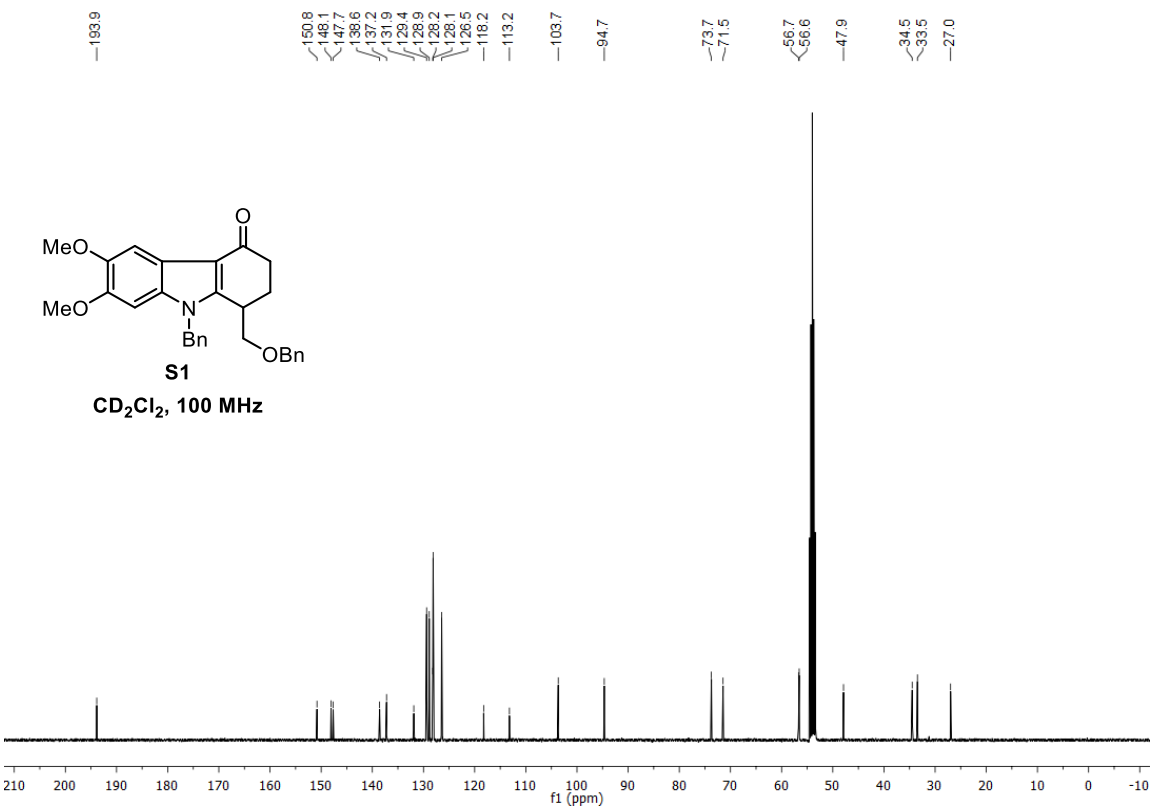


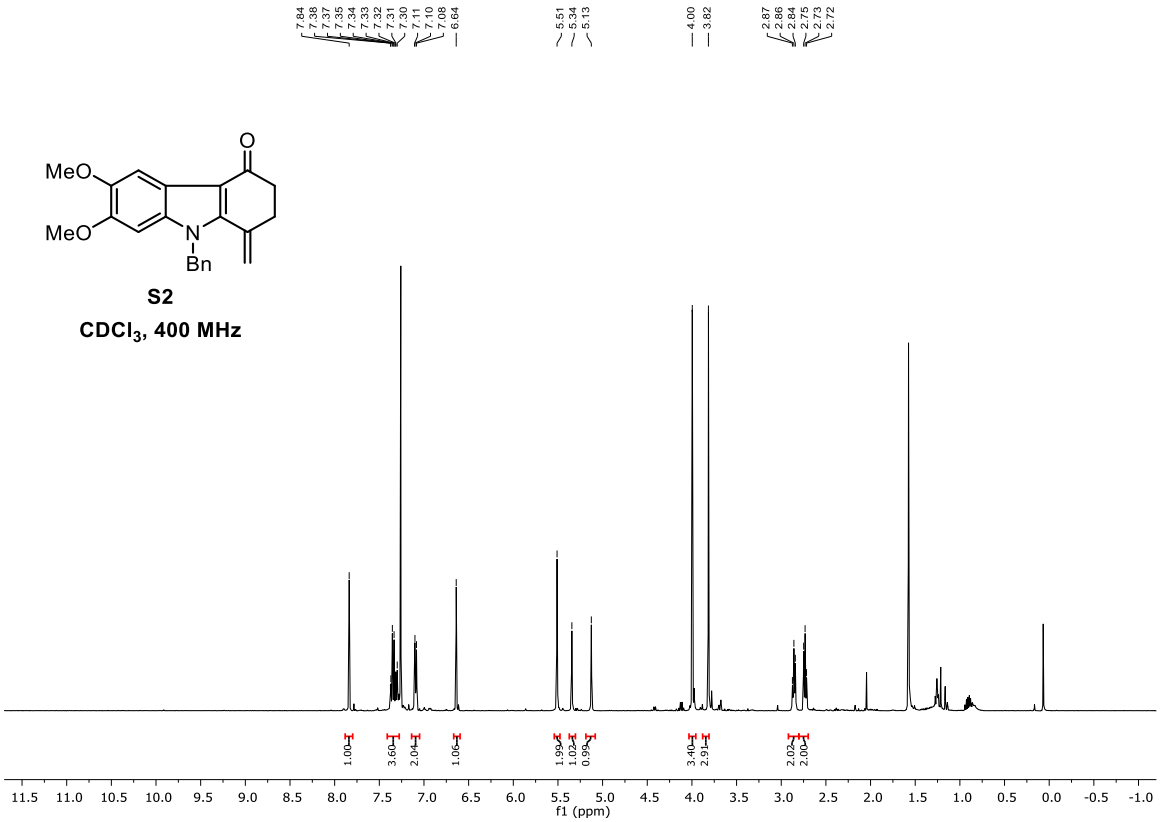


46

$CDCl_3$, 100 MHz

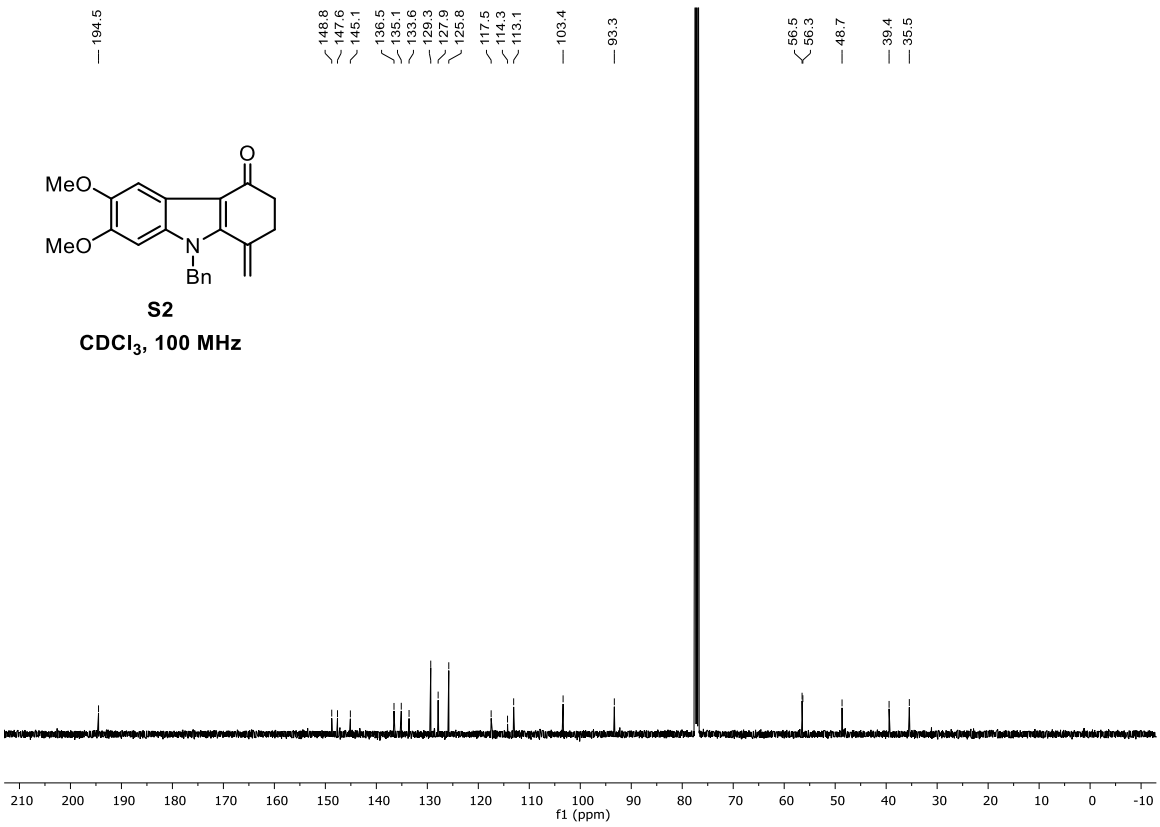

MeO
MeO
N
Bn
OBn
O
S1
CD2Cl2, 400 MHz
f1 (ppm)


MeO
MeO
N
Bn
OBn
O
S1
CD2Cl2, 100 MHz
f1 (ppm)



S2

$CDCl_3$, 400 MHz



S2

$CDCl_3$, 100 MHz

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